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SYNTHESIS OF POTENTIAL INSECTICIDES

AND

NEW SYNTHETIC APPLICATIONS OF VINAMIDINIUM AND
AZAVINAMIDINIUM SALTS: REACTIONS WITH REDUCING
AGENTS AND NITRO COMPOUNDS

BY

MICHAEL JOSEPH LIZZI
B.S., University of Central Florida, 1980

THESIS

Submitted in partial fulfillment of the requirements
for the Master of Science degree in Industrial Chemistry
in the Graduate Studies Program for the College of Arts and Sciences
University of Central Florida
Orlando, Florida

Spring Term
1982

ABSTRACT

This report discusses the research conducted in two areas: the synthesis of potential insecticides and the investigation of vinamidinium and azavinamidinium salt chemistry. Firstly, four classes of compounds were synthesized and characterized in the investigation of new potential insecticides. These classes of compounds include α -formamidine methyl esters, amidines, diacylhydrazines and 2,5-disubstituted-1,3,4-oxadiazoles and were characterized via NMR and infrared spectroscopy. This account also reveals and discusses the experimental conditions and procedures necessary for the preparation of these potential insecticides.

Secondly, the reaction of [3-(dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride (Gold's Reagent) with nucleophiles such as activated (nitro) methylene compounds was examined in hopes of obtaining a more economical process for the production of indoles. Optimum reaction conditions were determined to an extent with regard to solvent, base and temperature. In addition, the reduction of vinamidinium salts was examined using numerous reducing agents; however, only sodium borohydride and sodium cyanoborohydride were found to yield unique products, that is, N,N-dimethylallylic amines and 2-aryl-3-cyanoamines, respectively. Hence, this report also discloses the experimental conditions and procedures responsible for the novel synthesis of these products, and offers a probable mechanism for their formation. Finally, this report briefly explains the data, and offers recommendations for further research.

ACKNOWLEDGEMENTS

I am greatly indebted to Dr. John T. Gupton, III, for his guidance, patience, encouragement and availability throughout my graduate research, in addition to the knowledge and experience I acquired as a result of his expertise in Synthetic Organic research.

I am also grateful to Dr. John P. Idoux and Dr. Guy C. Mattson for their time and input as members of my thesis committee. In addition, I wish to thank Dow Chemical Company for supplying a grant which supported me financially and enabled the execution of this research.

I also wish to thank my family for their continued moral support throughout my college years. Finally, and most importantly, I wish to thank God for continued strength and guidance during the course of my research and college education (Deut. 31:8, Col. 3:17).

TABLE OF CONTENTS

	Page
ACKNOWLEDGEMENTS	iii
LIST OF TABLES	vi
LIST OF FIGURES	vii
LIST OF ABBREVIATIONS	viii

PART I

SYNTHESIS OF POTENTIAL INSECTICIDES

I. INTRODUCTION.	1
II. EXPERIMENTAL.	11
A. Preparation of α -Formamidine Methyl Esters	11
B. Preparation of Amidines Via Gold's Reagent	14
C. Preparation of Diacylhydrazines and Oxadiazoles, Potential Insecticides	17
1. Preparation of substituted methylbenzoates	17
2. Preparation of substituted benzhydrazides	20
3. Preparation of substituted diacylhydrazines	23
4. Preparation of 2,5-disubstituted-1,3,4- oxadiazoles	26
III. DISCUSSION OF RESULTS	28
IV. CONCLUSIONS	33
V. RECOMMENDATIONS	35

TABLE OF CONTENTS (Continued)

Page

PART II

NEW SYNTHETIC APPLICATIONS OF VINAMIDINIUM AND AZAVINAMIDINIUM SALTS: REACTIONS WITH REDUCING AGENTS AND NITRO COMPOUNDS

I.	INTRODUCTION	37
II.	EXPERIMENTAL	47
	A. Preparation of Nitroenamines Via Gold's Reagent	47
	B. Preparation of Arylvinamidinium Salts from Substituted Acetic Acids	49
	C. Reduction of Arylvinamidinium Perchlorates	51
	1. Reduction of arylvinamidinium perchlorates using sodium borohydride	51
	2. Reduction of anylvinamidinium perchlorates using sodium cyanoborohydride	53
III.	DISCUSSION OF RESULTS.	55
IV.	CONCLUSIONS	62
V.	RECOMMENDATIONS.	64
	INSTRUMENTATION AND EQUIPMENT	67
	REFERENCES	68

LIST OF TABLES

TABLES		PAGE
I.	Experimental Data for the Preparation of Formamidino Esters	11
II.	Experimental Data for the Preparation of Formamidines	14
III.	Experimental Data for the Preparation of Aryl Methyl Esters	17
IV.	Experimental Data for the Preparation of Hydrazides	20
V.	Experimental data for the Preparation of Diacylhydrazines	23
VI.	Experimental Data for the Preparation of Oxadiazoles	26
VII.	Optimization of Reaction Conditions for the Synthesis of Nitroenamines	47
VIII.	Experimental Data for the Preparation of Arylvinamidinium Perchlorates.	49
IX.	Experimental Data for the Preparation of N,N-Dimethylallylic Amines	51
X.	Experimental Data for the Preparation of 3-Cyanoenamines	53

LIST OF FIGURES

FIGURES		PAGE
1.	Mechanism for the preparation of formamidino esters from DMFA and α -amino acids	4
2.	Mechanism for the preparation of amidines from Gold's Reagent and primary amines	6
3.	Proposed synthetic scheme for the preparation of diacylhydrazines and 2,5-disubstituted-1,3,4-oxadiazoles	8
4.	Classes of compounds synthesized as potential insecticides	33
5.	Reaction of vinamidinium salts with electrophiles and nucleophiles	40
6.	Preparation of Gold's reagent from cyanuric chloride and DMF	41
7.	Preparation of enamines via DMFA and substituted toluenes	42
8.	Preparation of arylvinamidinium perchlorates from carboxylic acids and DMF	44
9.	Preparation of α,β -unsaturated ketones from enamminones via selective reduction using sodium borohydride	46
10.	Preparation of vinyl sulfides from thioenaminones via selective reduction using sodium borohydride	46
11.	Proposed mechanism for the formation of N,N-dimethylallylic amines from sodium borohydride reduction of arylvinamidinium salts	58
12.	Step 4 in the mechanism for the reduction of vinamidinium salts with sodium borohydride and sodium cyanoborohydride	59
13.	Proposed mechanism for the preparation of substituted styrenes from a nitroenamine and Grignard reagents	66

LIST OF ABBREVIATIONS

bp	boiling point
°C	degrees centigrade
cm ⁻¹	wave numbers
DMF	dimethylformamide
DMFA	dimethylformamide dimethyl acetal
DMSO	dimethylsulfoxide
ET ₃ N	triethylamine
g	grams
GLC	Gas-Liquid Chromatography
HMPA	hexamethylphosphoramide
hr	hours
Hz	Hertz (cycles per second, nmr spectrum)
iPrOH	isopropanol
IR	Infrared
J	coupling constant (nmr spectrum)
M ⁺	molecular ion (mass spectrum)
m/e	mass to change ratio (mass spectrum)
MeOH	methanol
min	minutes
ml	milliliters
mm	millimeters
mol	mole

LIST OF ABBREVIATIONS (Continued)

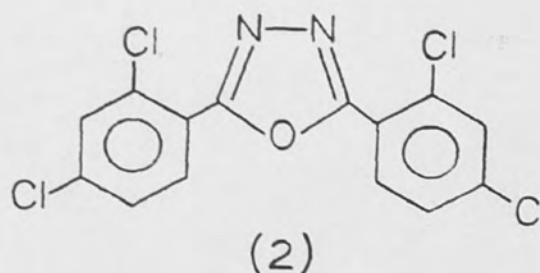
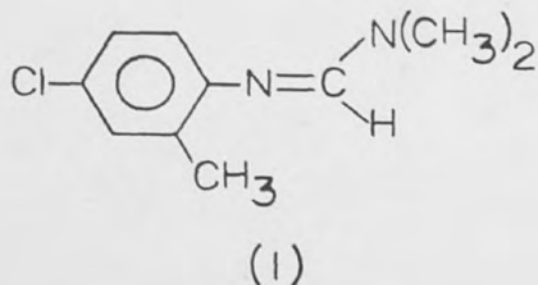
mp	melting point
NaOiPr	sodium isopropoxide
NaOtBu	sodium tertiary butoxide
NMR	Nuclear Magnetic Resonance
PPA	polyphosphoric acid
ppm	parts per million (nmr spectrum)
tBuOH	tert-butanol
THF	tetrahydrofuran

PART I

SYNTHESIS OF POTENTIAL INSECTICIDES

I. INTRODUCTION

In recent years, considerable interest on the part of various international chemical companies has been displayed in insecticide research due to problems (e.g. degradation properties and toxicity) with current insecticides, and the desire to obtain insecticides with greater biological activity. For example, toxicity problems with the currently commercialized formamidine insecticide, chlorodimeform (1),¹ have contributed to the interest in new insecticides. Chlorodimeform has been found to form the toxic metabolite 2-amino-5-chloro-toluene. In addition, the symmetrical 1,3,4-oxadiazole, DOWCO 416 (2),² is a larvacide and was found to be biologically active against manure-breeding insects such as houseflies, face flies and hornflies;



however, a larvacide with enhanced activity is desired. It has also been noted in the patent and chemical literature that various functional

groups have not as yet been incorporated into the formamide insecticides. For the above reasons, the investigator proposes the synthesis and testing of various formamidine insecticides including α -amino acid analogs, aromatic heterocyclic analogs and unsaturated fatty acid type analogs. Also, this investigator proposes to synthesize DOWCO 416 similogs and their precursors, diacylhydrazines, which may prove to possess better biological properties than DOWCO 416 itself. The formamidines and possibly the oxadiazoles could then be screened in vitro for their inhibition of monoamine oxidase, an enzyme responsible for controlling the level of biogenic amines. Some researchers have argued that toxicity to the insect is due to the inhibition of monoamine oxidase. Consequently, the objective of this research (Part I) is to synthesize and characterize potential insecticides, namely, α -formamidine methyl esters, N,N-dimethyl-N'-substituted formamidines, and both substituted diacylhydrazines and 2,5-disubstituted-1,3,4-oxadiazoles.

Firstly, a number of formamidine analogs related to chlorodimeform will be prepared, namely, α -amino acid, heterocyclic and unsaturated fatty acid type analogs. A series of α -formamidine methyl esters will be prepared and purified from reaction of a series of α -amino acids with N,N-dimethylformamide dimethyl acetal (DMFA). It was found by J. Fitt and H. Gschwend³ that an essentially quantitative conversion to the amidino ester could be achieved by refluxing a solution containing an α -amino acid in 2-2.5 equivalents of DMFA, during which the methanol byproduct was removed by distillation. They performed this reaction with four amino acids, two of which will be prepared here (dl-methionine

and dl-phenylalanine). In addition, nine other amino acids will be prepared (Table I). The mechanism for this reaction is believed to proceed through carbonium ion intermediates (Figure 1) and requires one mole of DMFA for each acid or amine group converted to an ester or N,N-dimethylaminomethylene group respectively. The formamidino esters will be purified by vacuum distillation and analyzed by NMR, IR, mass spectrometry and gas-liquid chromatography (glc). J. Thenot and E. Horning have performed GC and GC-MS studies on several formamidino esters,⁴ thereby aiding in the characterization of these compounds.

The heterocyclic formamidines and fatty acid type formamidine will be synthesized via "Gold's reagent" (3) and primary amines. The azavinamidinium salt (3) will be referred to as Gold's reagent in order to simplify its nomenclature. Although aromatic, heterocyclic and other amidines may be prepared from their respective amines and N,N-dimethylformamide dialkyl acetals,⁵⁻⁷ recent technology has been developed by Gupton⁸ and coworkers whereby Gold's reagent produced identical products in higher yields and under milder conditions. In addition, Gold's reagent is much cheaper than formamide acetals resulting in a more economical synthesis of amidines. Thus, Gold's reagent will be prepared and utilized as the formylating agent of amines. The preparation and reaction of Gold's reagent and vinamidinium salts will be discussed in more detail in the introduction of Part II. The heterocyclic and unsaturated fatty acid type formamidines will be prepared by allowing Gold's reagent to react with the amine in a sodium methoxide-methanol solution. The reaction will be conducted using 15% excess of the amine

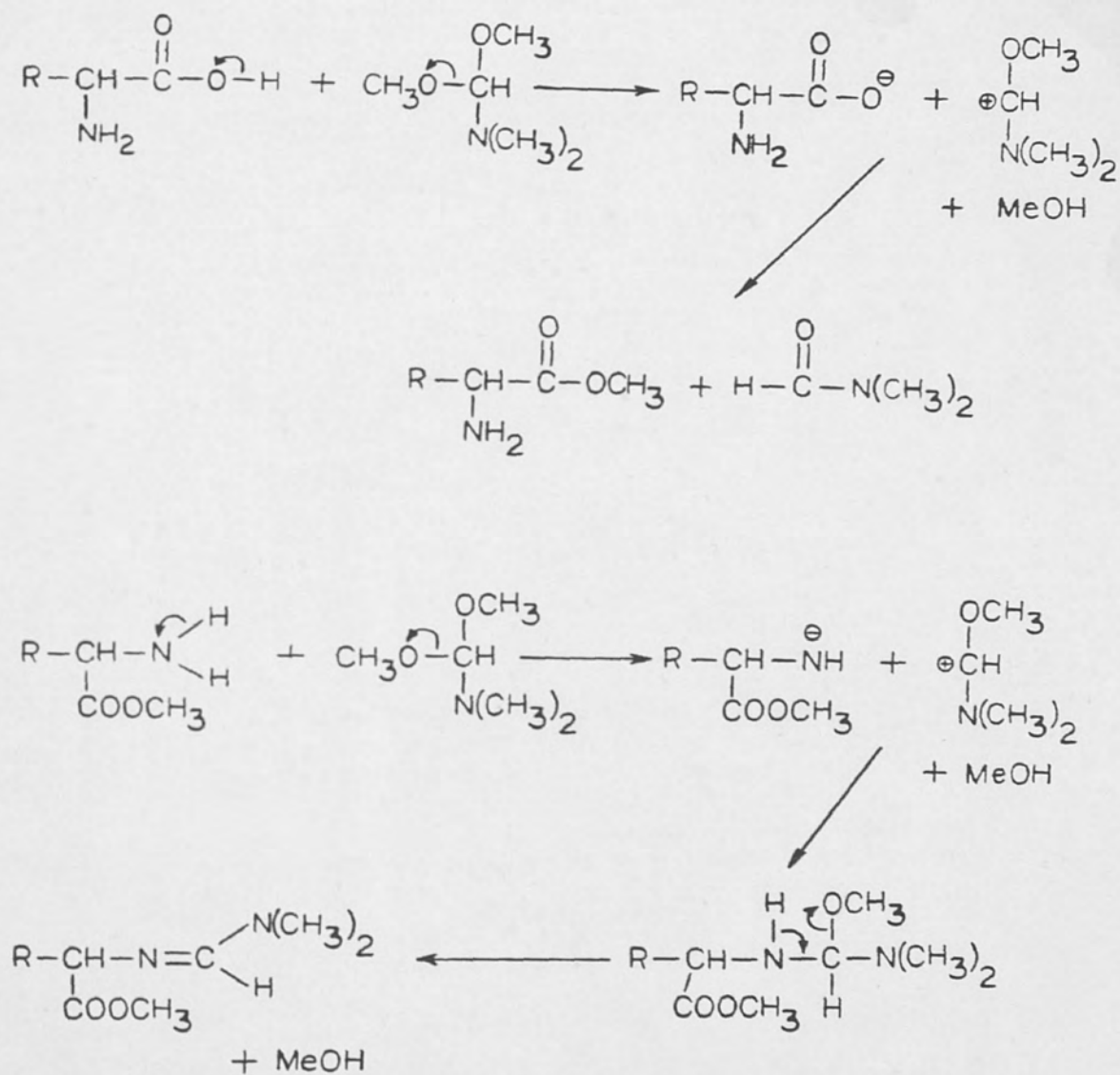
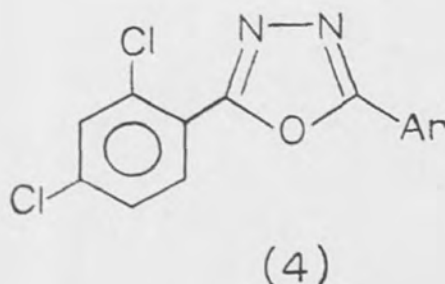


Figure 1. Mechanism for the preparation of formamidino esters from DMFA and α -amino acids.

and sodium methoxide while refluxing overnight. The mechanism ⁸ is believed to occur as seen in Figure 2 where N,N-dimethylformamidine is a better leaving group than the N,N-dimethylamino group. NMR and infrared spectroscopy will be employed for the characterization of all formamidine analogs prepared.

Secondly, a series of substituted diacylhydrazines (6) and 2,5-disubstituted-1,3,4-oxadiazoles (7) will be synthesized as potential pesticides and will be assayed for larvacide activity (see Figure 3). Currently, certain oxadiazoles are used for the control of manure-breeding insects. These oxadiazoles have been disclosed in a 1980 patent ² and are exhibited by the following formula (4):



where Ar represents phenyl, 2-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl, 4-methylphenyl, 4-cyanophenyl, 2,4-dichlorophenyl or 3,5 dichlorophenyl. It is believed that both the 2,4-dichloro-phenyl and oxadiazole moieties are largely responsible for the biological activity of these substances. Since other oxadiazoles may very well possess greater biological activity it is the purpose of the investigator to synthesize similogs of the above compounds and

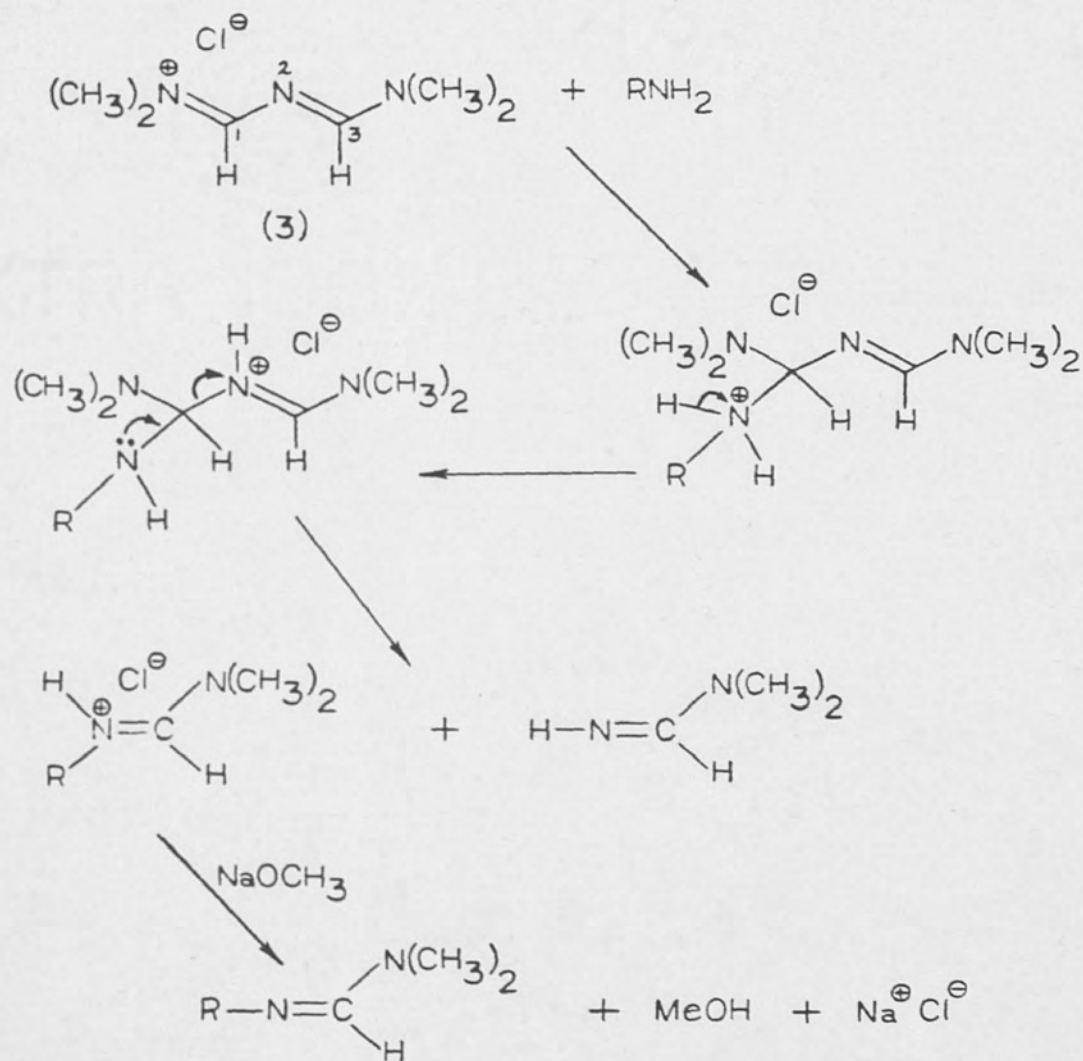


Figure 2. Mechanism for the preparation of amidines from Gold's reagent and primary amines.

forward them to DOW Chemical Company for biological screening. In addition to preparing structural isomers of the above active compounds, derivatives will be prepared and tested where Ar is equal to 2-methoxyphenyl and 3-methoxyphenyl. It is conceivable that the methoxy group will create a molecule having increased hydrophobic or lipophilic character. This may result in a molecule having greater solubility in the cell membranes of insects. The precursors of the oxadiazoles, diacylhydrazines, will also be screened due to their similarity in structure and properties with oxadiazoles. Some researchers have attributed the high activity of certain hydrazide derivatives to the diacylhydrazine center.⁹ The reaction sequence exhibited on the following page (Figure 3) is proposed for the preparation of these potential insecticides.

The feasibility of this proposed synthetic scheme will be examined by preparing an already known biologically active oxadiazole (entry 1, Tables III-VI), 2-(2,4-dichlorophenyl)-5-phenyl-1,3,4-oxadiazole, and confirming its structure via spectral data. This would then ensure that the above synthetic route is a general method for the preparation of most if not all simiologs. Also, preparing the above compound would make available the spectral data which are characteristic of all subsequently prepared intermediates and oxadiazoles. This route was chosen since it would provide unambiguously, the desired unsymmetrical 2,5-disubstituted oxadiazoles and at the same time the unsymmetrical diacylhydrazine precursors. Thus, both types of compounds could be synthesized and assayed for pesticide activity.

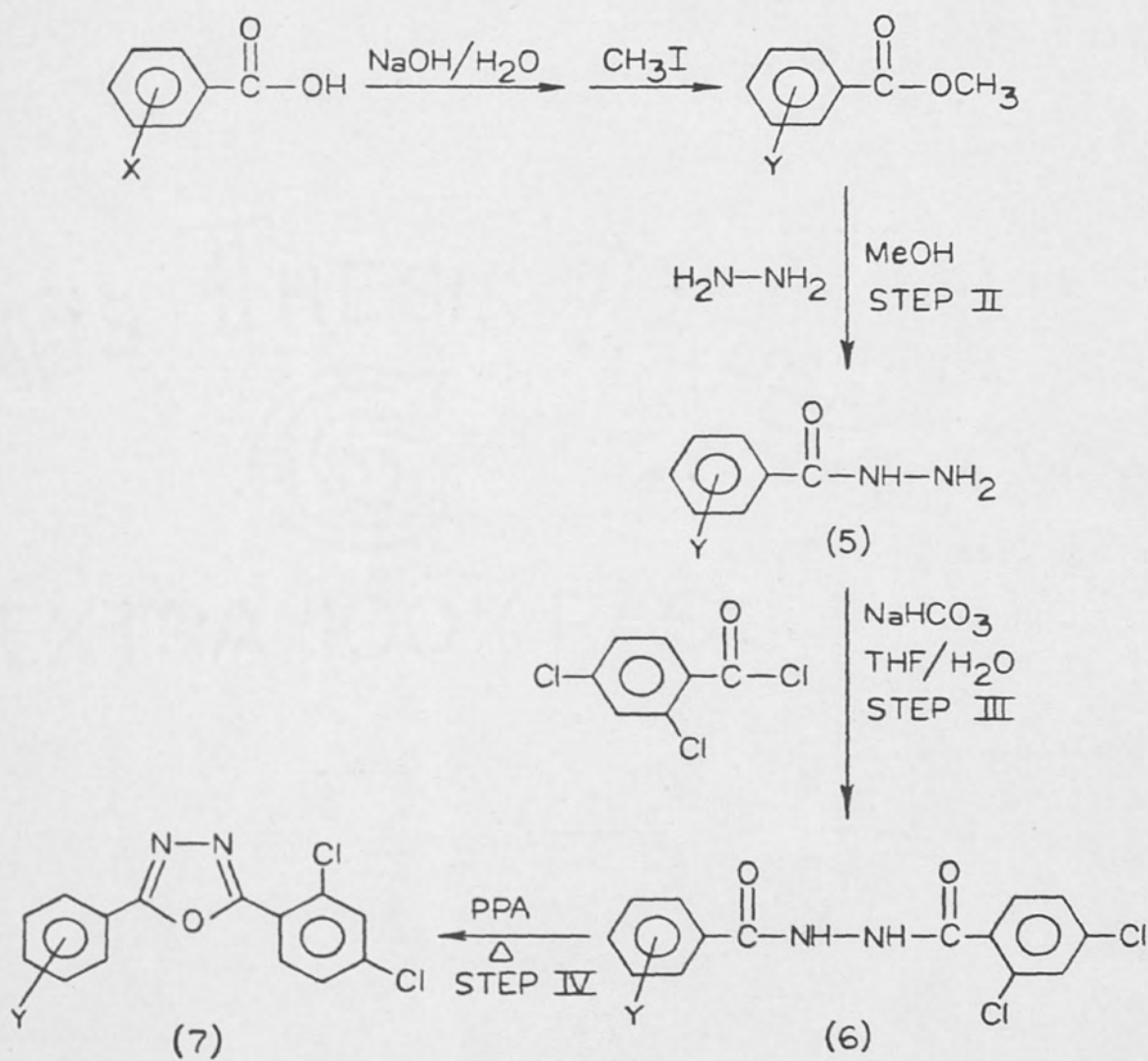


Figure 3. Proposed synthetic scheme for the preparation of diacylhydrazines and 2,5-disubstituted-1,3,4-oxadiazoles.

In the chosen reaction sequence (Figure 3) a substituted carboxylic acid will be treated with a 25% sodium hydroxide solution in hexamethylphosphoramide (HMPA). This solution will then be treated with methyl iodide at room temperature, thereby forming the appropriate methyl benzoate in quantitative yield.¹⁰ The ester would then be reacted with anhydrous hydrazine in methanol at reflux where a solid, the hydrazide (5), will readily form by crystallization when reaching room temperature or by inducing crystallization (i.e. etching the flask). This reaction is a nucleophilic substitution where the methoxy group is the leaving group. In step III, a benzoyl chloride is subsequently added dropwise to a THF/H₂O mixture containing the hydrazide. The diacylhydrazine (6) should readily form and crystallize out of solution under mild conditions. Sodium bicarbonate is used in this step to neutralize the byproduct, hydrochloric acid. Cyclization of the diacylhydrazine into the oxadiazole (7) can be accomplished via polyphosphoric acid (PPA), although phosphoroxychloride¹¹ has also been used as a dehydrating agent. NMR and infrared spectroscopy will be employed for the characterization of all key compounds in Figure 3, the latter technique proving most important.

A review of the nomenclature¹², preparation^{13,14}, properties^{12,14} and reactions^{12,14} of hydrazides (5) and diacylhydrazines (6) are available. Also excellent reviews on the preparation properties and reactions of 1,3,4-oxadiazoles may be consulted.^{11,15,16} One should note that the 1,3,4-oxadiazoles to be synthesized may also have potential application in drug syntheses, production of thermostable polymers, preparation of dyes, photography and in other fields of science and technology.^{11,16}

Finally, all of the aforementioned potential pesticides will be sent to the Agriculture Research Department of DOW Chemical for biological studies. ~~11,16~~

II. EXPERIMENTAL

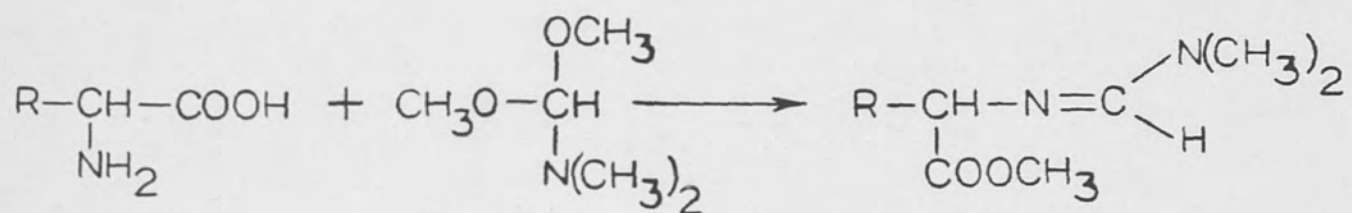
A. Preparation of α -Formamidino-Methyl Esters

Table I

Experimental Data for the Preparation of Formamidino Esters^a

Entry	R	Yield ^b (%)	bp or mp, °C (mm Hg)	molar ratio acetal:amino acid
1	$-\text{CH}_3^c$	72	53-58 (0.3)	2.5:1
2	$-\text{CH}(\text{CH}_3)_2^d$	93	65 (0.5)	2.5:1
3	$-\text{CH}_2\text{CH}(\text{CH}_3)_2^e$	86	70-76 (0.5)	2.5:1
4	$-(\text{CH}_2)_2\text{S}(\text{CH}_3)^f$	87	95 (0.5)	2.5:1
5	$-\text{CH}(\text{CH}_3)(\text{C}_2\text{H}_5)^g$	96	66-80 (0.4)	2.5:1
6	$-\text{CH}_2\text{COOH}^h$	65	89-93 (0.2)	3.5:1
7	$-\text{CH}_2\text{CH}_2\text{COOH}^i$	74	100-106 (0.5)	3.5:1
8	$-(\text{CH}_2)_4\text{NH}_2^j$	74	127-140 (0.2)	4.0:1
9	$-\text{CH}_2(\text{C}_6\text{H}_5)^k$	87	99-104 (0.2)	3.5:1
10	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{OH}^l$	55	136-148 (0.2)	4.0:1
11	$-\text{CH}_2-\text{Im}^m$	40	162-171	3.5:1

- a. For every carboxylic acid group converted into a methyl ester group, one mole of methanol and one mole of DMF are released. Also, for every primary amine group converted into a formamidine group, two moles of methanol are released.
- b. The yields refer to products purified by either vacuum distillation or recrystallization.
- c. NMR (CDCl_3) δ 1.16-1.40 (d, 3H), 2.83 (s, 6H), 3.63 (s, 3H), 3.65-4.02 (q, 1H) and 7.35 (s, 1H); IR (thin film) 1740 and 1640 cm^{-1} .
- d. NMR (CDCl_3) δ 0.71-1.04 (d, 6H), 1.62-2.44 (m, 1H), 2.85 (s, 6H), 3.21-3.44 (d, 1H), 3.66 (s, 3H) and 7.27 (s, 1H); IR (thin film) 1740 and 1650 cm^{-1} .
- e. NMR (CDCl_3) δ 0.72-1.04 (m, 6H), 1.44-1.77 (m, 3H), 2.84 (s, 6H), 3.62 (s, 3H), 3.60-3.90 (m, 1H) and 7.30 (s, 1H); IR (thin film) 1740 and 1650 cm^{-1} .
- f. See reference 3 for spectral data of this compound.
- g. NMR (CDCl_3) δ 0.71-1.05 (m, 6H), 1.05-2.27 (m, 3H), 2.86 (s, 6H), 3.32-3.60 (m, 1H), 3.69 (s, 3H) and 7.27 (s, 1H); IR (thin film) 1740 and 1650 cm^{-1} .
- h. The product of this reaction is a di-methylester where four moles of methanol and two moles of DMF are liberated for every mole of amino acid reacted. This compound is a solid and melts at 50-55°C. NMR (CDCl_3) δ 2.70-2.90 (d, 2H), 2.90 (s, 6H), 3.72 (s, 3H), 3.78 (s, 3H), 4.09-4.40 (t, 1H) and 7.51 (s, 1H); IR (CHCl_3) 1740 and 1650 cm^{-1} .
- i. This product is also a di-methylester. NMR (CDCl_3) δ 1.70-2.52 (m, 4H), 2.85 (s, 6H), 3.61 (s, 3H), 3.64 (s, 3H), 3.59-3.89 (m, 1H) and 7.37 (s, 1H); IR (thin film) 1740 and 1640 cm^{-1} .
- j. The amino acid utilized (lysine) was in the form of a hydrochloride, and therefore first converted to a free base by reaction with sodium methoxide, thereby eliminating methanol and sodium chloride. The product of this reaction is a di-formamidine. NMR (CDCl_3) δ 1.09-2.18 (broad m, 6H), 2.83 (s, 6H), 2.89 (s, 6H), 3.07-3.42 (t, 2H), 3.57-3.89 (m, 1H), 3.69 (s, 3H), 7.41 (s, 1H) and 7.46 (s, 1H); IR (thin film) 1740 and 1650 cm^{-1} .
- k. See the experimental procedure below for spectral data.
- l. The product of this reaction is an aryl methyl ether (derivative of anisole) as well as a formamidino ester. NMR (CDCl_3) δ 2.68 (s, 6H), 2.91-3.17 (m, 2H), 3.57 (s, 3H), 3.65 (s, 3H), 3.73-4.07 (m, 1H), 6.63-6.92 (d, $J=8\text{Hz}$, 2H), 6.98-7.26 (d, $J=8\text{Hz}$, 2H) and 7.04 (s, 1H); IR (thin film) 1740, 1650, 1590 and 1250 cm^{-1} .

- m. This product was recrystallized by a hexane-chloroform mixture at room temperature affording a beige solid. NMR (D_2O/DSS) 2.86-3.32 (d, 8H), 4.09-4.41 (m, 1H), 4.78 (s, 3H), 6.98 (s, 1H), 7.54 (s, 1H) and 7.74 (s, 1H); IR (KBr) 1740 and 1600 cm^{-1} .

dl-Methyl N-(Dimethylaminomethylene)phenylalanate

To a 100 ml, one-necked, round-bottomed flask was added 4.1g (0.025 mol) of dl-phenylalanine and 10.4g (0.0825 mol) of N,N-dimethylformamide dimethyl acetal. The equipment consisted of the flask, distillation head, vacuum adapter, 50-ml collecting flask, drying tube containing Drierite, stirring bar, thermometer adapter and thermometer. The reaction mixture was heated for 3 hours while observing a vapor temperature of 65°C; methanol was distilled during the reaction. The reaction was terminated when the temperature decreased to a minimum (~45-55°C). This signified that all of the methanol was distilled and that the temperature would soon increase drastically. The reaction mixture was cooled to room temperature. Byproduct DMF and any unreacted DMFA were then distilled in vacuo at ~45°C and 0.5 mm Hg. Finally the formamidino ester was distilled (Kugelrohr) at 99-104°C @ 0.2 mm Hg where 5.4g (87% yield) of light yellow liquid was obtained: lit.³ bp 124-126°C @ 0.6 mm Hg; NMR ($CDCl_3$) δ 2.77 (s, 6H), 2.84-3.20 (t, 2H), 3.54 (s, 3H), 3.71-4.04 (t, 1H), 6.99 (s, 1H) and 7.18 (s, 1H); IR (thin film) 1735 (C=O ester stretch) and 1640 cm^{-1} (C-N stretch).

B. Preparation of Amidines Via "Gold's Reagent"

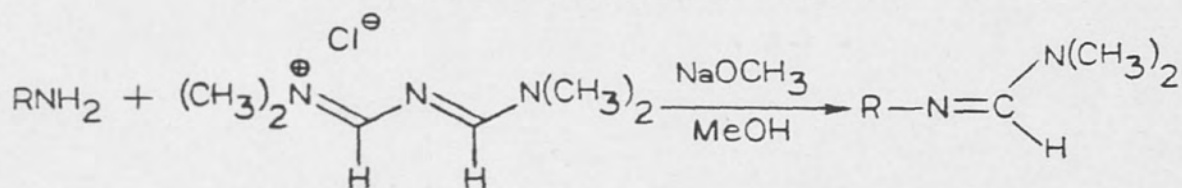
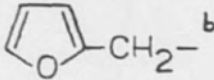
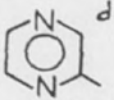
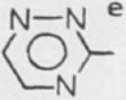


Table II

Experimental Data for the Preparation of Formamidines

Entry	R	Yield ^a (%)	bp or mp, °C (mm Hg)
1		67	59-65 (0.3)
2	$\text{CH}_3-(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_8-$ ^c	78	142-154 (0.3)
3		68	89-98 (0.6)
4		45	>230

- a. The yield reported in entries 1-3 refer to yields after distillation.
- b. NMR (CDCl_3) δ 2.76 (s, 6H), 4.36 (s, 2H), 6.02-6.32 (m, 2H) and 7.23-7.35 (broad s, 2H); IR (thin film) 1640, 1590 and 1370 cm^{-1} .
- c. See experimental procedure below for spectral data.

- d. NMR (CDCl_3) δ 3.07 (s, 6H), 8.13-8.33 (broad s, 2H), 8.45 (broad s, 1H) and 8.67 (broad s, 1H); IR (thin film) 1630 ($\text{C}=\text{N}$), 1570 (aromatic $\text{C}=\text{C}$), 1380 (aromatic $\text{C}-\text{N}$) and 1350 cm^{-1} ($\text{C}-\text{N}$ stretch).
- e. The product from this reaction is not fully characterized at this time since a solvent system for recrystallization has yet to be determined, thus the yield reported refers to crude yield. Although the dimethylamino peak is present in the NMR spectrum, there is some doubt that the desired product was synthesized since the formamidino hydrogen peak is unaccounted for. NMR (CDCl_3) δ 3.32 (s, 6H), 8.97 (s, 1H) and 9.96 (s, 1H).

N,N-Dimethyl-N'-oleyformamidine

The equipment consisted of a 250 ml, three-necked, round-bottomed flask, reflux condenser, thermometer adapter, thermometer, stirring bar, glass stopper and mineral oil bubbler. A nitrogen atmosphere was maintained at all times.

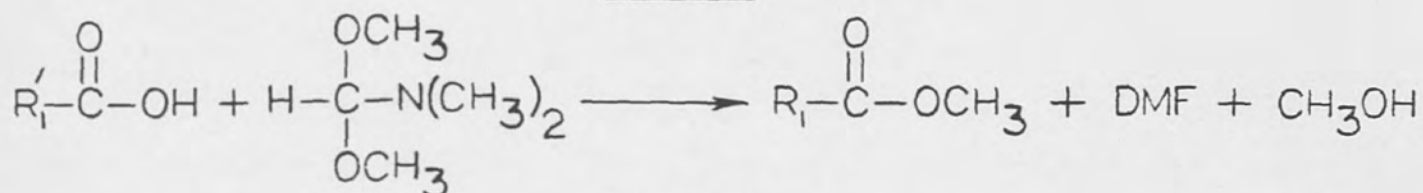
A solution of sodium methoxide in methanol was prepared by the addition of 1.5g (0.065 mol) of sodium metal to the flask containing 100 ml of absolute methanol. After all of the sodium had reacted (10 min.), the solution was cooled to room temperature and 13.4g (0.050 mol) of oleylamine was added in one portion. The resulting solution was stirred for several minutes whereupon 10.6g (0.065 mol) of Gold's Reagent (3) was added and the resulting mixture was refluxed with stirring overnight. The reaction mixture was cooled to room temperature and the solvent removed via a rotating evaporator. The residue was dissolved in 100 ml of chloroform and extracted twice with 30 ml portions of saturated sodium bicarbonate solution. The chloroform phase was dried over anhydrous sodium sulfate for 20-30 min. and filtered. Chloroform was then removed in vacuo to afford 20.3g of liquid. The material was distilled (Kugelrohr) to produce 12.6g (78% yield) of the formamidine as

an orange-gold liquid: bp 142-154°C (0.3 mm); NMR (CDCl_3) δ 0.89 (t, 3H), 1.29 (broad s, 24H), 1.80-2.25 (m, 4H), 2.77 (s, 6H), 3.03-3.36 (t, 2H), 5.20-5.48 (t, 2H) and 7.22 (s, 1H); IR (thin film) 1640 (C=N stretch), 1360 (C-N stretch) and 960 cm^{-1} ($\text{H}-\text{C}=\text{C}-\text{H}$).

C. Preparation of Diacylhydrazines and Oxadiazoles,
Potential Insecticides

1. Preparation of substituted methyl benzoates

METHOD A



METHOD B

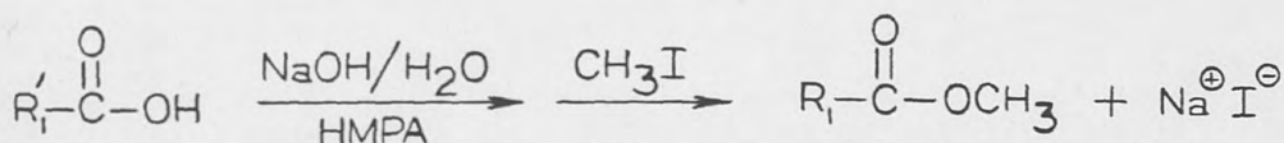


Table III

Experimental Data for the Preparation of Aryl Methyl Esters

Entry	R ₁	R ₁	Method	Yield ^a (%)
1	2,4-dichlorophenyl	2,4-dichlorophenyl	A	69 ^b
2	2-hydroxyphenyl	2-methoxyphenyl	A	~90 ^c
3	3-hydroxyphenyl	3-methoxyphenyl	B	79 ^d
4	2-fluorophenyl	2-fluorophenyl	B	86 ^e
5	3-fluorophenyl	3-fluorophenyl	B	90 ^f
6	2-(trifluoromethyl)phenyl	2-(trifluoromethyl)phenyl	B	100 ^g
7	3-(trifluoromethyl)phenyl	3-(trifluoromethyl)phenyl	B	100 ^h

a. The yields reported refer to crude yields unless otherwise specified.

- b. This yield refers to distilled ester (bp = 63-85°C @ 0.06 mm Hg); NMR (CDCl₃) δ 3.90 (s, 3H), 7.22 (d of d, J=8Hz, J=2Hz, 1H), 7.36 (d, J=2Hz, 1H) and 7.72 (d, J=8Hz, 1H); IR (thin film) 1730, 1590, 1470, 1430, 840, 780 and 770 cm⁻¹.
- c. The actual yield is unknown since a small amount of DMF remained upon distillation as seen by NMR Spectroscopy; NMR (CDCl₃) δ 3.85 (s, 3H), 3.90 (s, 3H) and 6.80-7.90 (m, 4H); IR (thin film) 1725, 1600, 1580, 1490, 1460 and 750 cm⁻¹.
- d. As in c above, at least two moles of sodium hydroxide and methyl iodide are required for every mole of hydroxybenzoic acid due to conversion of the hydroxy group to the methoxy group; NMR (CDCl₃) 3.78 (s, 3H), 3.87 (s, 3H) and 6.88-7.74 (m, 4H); IR (thin film) 1725, 1600, 1590, 1490, 1450, 780 and 750 cm⁻¹.
- e. NMR (CDCl₃) δ 3.92 (s, 3H) and 6.92-8.09 (m, 4H); IR (thin film) 1720, 1610, 1470, 1450 and 750 cm⁻¹.
- f. See experimental procedure below for spectral data.
- g. This reaction and the reaction in entry 7 were conducted by Dr. John T. Gupton and included for completeness. Both esters probably contained some carbon tetrachloride resulting in higher than normal yields. NMR (CDCl₃) δ 3.94 (s, 3H) and 7.46-7.93 (m, 4H); IR (thin film) 1725, 1600, 1580, 1430 and 760 cm⁻¹.
- h. NMR (CDCl₃) δ 3.98 (s, 3H) and 7.37-8.42 (m, 4H); IR (thin film) 1725, 1600, 1430 and 760 cm⁻¹.

Methyl 3-Fluorobenzoate

To a 250-ml Erlenmeyer flask was added 14.0g (0.10 mol) of m-fluorobenzoic acid and 75 ml of HMPA. To this solution was added 4.4g (0.11 mol) of sodium hydroxide (25% aqueous solution) with stirring. This solution was stirred at room temperature with a stirring bar for one hour whereupon 10 ml of water and then 28.4g (0.20 mol) of methyl iodide (100% excess) were added. The water was necessary to dissolve the sodium salt that had precipitated. The resulting solution was stirred at room temperature for two hours. The reaction mixture was poured into a 500-ml separatory funnel containing 100 ml of a 5%

hydrochloric acid solution. This aqueous system was extracted with three 75 ml portions of anhydrous ethyl ether. The combined ether extracts were washed with 60 ml of saturated sodium bicarbonate and then 60 ml of water. The extract was dried over anhydrous magnesium sulfate, filtered and concentrated at reduced pressure yielding 13.9g (90% yield) of a reddish-orange liquid¹⁰ which was found to be ~100% pure by GLC; NMR (CDCl₃) δ 3.89 (s, 3H) and 6.99-7.91 (m, 4H); IR (thin film) 1720 (C=O ester stretch), 1590, 1480, 1450 (aromatic C=C), 780 (m-subst'd ring) and 750 cm⁻¹ (aromatic C-H).

2. Preparation of substituted benzhydrazides

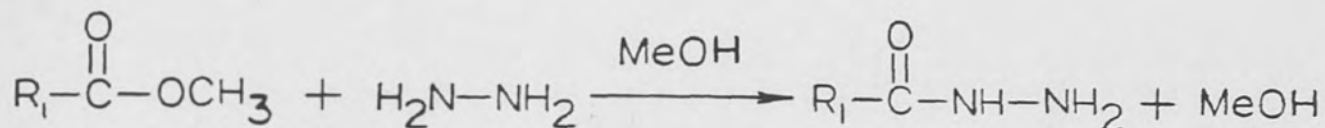


Table IV

Experimental Data for the Preparation of Hydrazides

Entry	R ₁	Yield ^a (%)
1	2,4-dichlorophenyl	98 ^b
2	2-methoxyphenyl	76 ^c
3	3-methoxyphenyl	83 ^d
4	2-fluorophenyl	93 ^e
5	3-fluorophenyl	64 ^f
6	2-(trifluoromethyl)phenyl	57 ^g
7	3-(trifluoromethyl)phenyl	93 ^h

a. Yields reported refer to crude yields unless otherwise specified.

b. The yield for this reaction was 56% when using 10% molar excess hydrazine and water in MeOH. NMR (d₆-DMSO) δ 4.43 (broad s, 2H), 7.30-7.60 (m, 3H) and 9.60 (broad s, 1H); IR (CHCl₃) 3430, 3320, 1670, 1620, 1580 and 1450 cm⁻¹.

c. This reaction was carried out using a 10% molar excess of water in hopes of forming the hydrate of hydrazine.¹³ Thus, one may ascertain from the data in Table IV that anhydrous conditions result in higher yields and are therefore preferable. NMR (d₆-DMSO) δ 3.88 (s, 3H), 4.33 (broad s, 2H), 6.83-7.94 (m, 4H) and 9.19 (broad s, 1H); IR (CHCl₃) 3420, 3320, 1650, 1620, 1600, 1480 and 1020 cm⁻¹.

- d. See experimental procedure below for spectral data.
- e. NMR (d^6 -DMSO) δ 4.75 (broad s, 2H) and 6.93-7.93 (m, 4H); IR ($CHCl_3$) 3460, 3320, 1650, 1610 and 1470 cm^{-1} .
- f. NMR (d^6 -DMSO) δ 3.76 (broad s, 2H) and 7.24-7.86 (m, 4H); IR ($CHCl_3$) 3440, 3320, 1660, 1620, 1580 and 1470 cm^{-1} .
- g. This yield refers to recrystallized product (solvent system = ETOH/ H_2O). This reaction and the reaction in entry 7 were conducted by Dr. John T. Gupton and included for completeness. NMR (d^6 -DMSO) δ 3.88 (broad s, 2H) and 7.38-7.92 (m, 4H); IR ($CHCl_3$) 3440, 3320, 1670, 1620, 1580 and 1470 cm^{-1} .
- h. NMR (d^6 -DMSO) δ 4.27 (broad s, 2H) and 7.38-8.33 (m, 4H); IR ($CHCl_3$) 3440, 3320, 1670, 1620, 1590 and 1470 cm^{-1} .

3-Methoxybenzhydrazide

The following procedure resulted in the most favorable results. The equipment consisted of a 250-ml, three-necked, round-bottomed flask, condenser, thermometer adapter, thermometer, teflon-coated stirring bar, drying tube containing Drierite and a 100-ml addition funnel. To the flask was added 1.8g (0.053 mol) of 97% anhydrous hydrazine (which was weighed directly into the flask in a hood), and 50 ml of absolute methanol. While stirring this solution at room temperature, 8.0g (0.048 mol) of methyl 3-methoxybenzoate was added dropwise from an addition funnel. The reaction mixture was refluxed overnight. After cooling the flask the methanol was removed using a rotating evaporator. Upon removal of the solvent a orange-yellow viscous liquid was obtained which subsequently crystallized upon etching of the flask (other analogs may require reheating of the residue with additional hydrazine). The solid was filtered, washed with hexane, water and then hexane to remove any starting material or impurities. As expected, 3-methoxybenzhydrazide was found to be soluble in 5% hydrochloric acid solution.¹⁷ Finally,

the solid was dried using a vacuum pump at ~ 0.3 mm Hg yielding 6.6g (83% yield) of a white solid; NMR (d^6 -DMSO) δ 3.82 (s, 3H), 3.94-4.43 (broad s, 2H), 6.86-7.62 (m, 4H) and 9.80 (broad s, 1H); IR ($CHCl_3$) 3440 (N-H stretch 1° amine), 3320 (N-H stretch 2° amide), 1670 (C=O amide stretch), 1620 (N-H bending 1° amine), 1600, 1580, 1470 (aromatic C=C) and 1040 cm^{-1} (aromatic ether).

3. Preparation of substituted diacylhydrazines

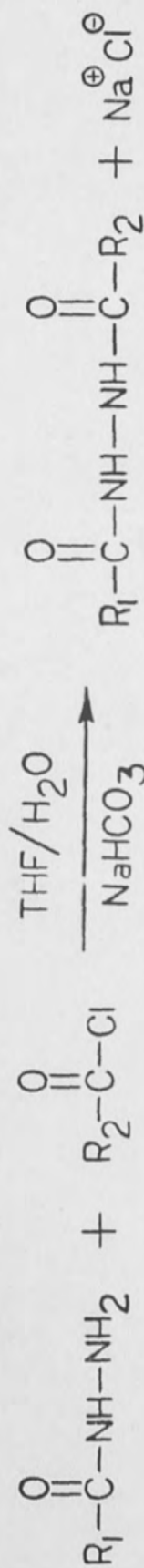


Table V

Experimental Data for the Preparation of Diacylhydrazines

Entry	R ₁	R ₂	Temp (°C)	Yield ^a (%)	mp (°C)	
					crude	recryst.
1	2,4-dichlorophenyl ^b	phenyl	rt*	94	2195-2205	—
2	2-methoxyphenyl ^c	2,4-dichlorophenyl	31	90	155-165	182-184
3	3-methoxyphenyl ^d	2,4-dichlorophenyl	rt	88	174-175	—
4	2-fluorophenyl ^e	2,4-dichlorophenyl	rt	100	189-191	—
5	3-fluorophenyl ^f	2,4-dichlorophenyl	31	98	198-201	—
6	2-(trifluoromethyl)phenyl ^g	2,4-dichlorophenyl	35	95	—	223-224
7	3-(trifluoromethyl)phenyl ^h	2,4-dichlorophenyl	rt	85	199-201	—

*rt = room temperature

- a. The yields reported refer to crude yields unless otherwise specified.
- b. NMR (d^6 -DMSO) δ 3.30 (s, 2H), 7.32-7.73 (m, 5H) and 7.86-8.16 (m, 3H); IR ($CHCl_3$) 340, 1630, 1590, 1430 and 870 cm^{-1} .
- c. See experimental procedure below for spectral data.
- d. NMR (d^6 -DMSO) δ 3.85 (s, 2H) and 6.99-7.84 (m, 7H); IR ($CHCl_3$) 3380, 1630, 1580, 1450, 1040 and 870 cm^{-1} .
- e. The true yield for this reaction, as well as that in entry 5 is probably 90+% since these products were not completely dry as seen by the NMR spectrum. NMR (d^6 -DMSO) δ 3.40 (s, 2H), 7.11-7.81 (m, 7H); IR ($CHCl_3$) 3400, 1620, 1580, 1450 and 870 cm^{-1} .
- f. NMR (d^6 -DMSO) δ 3.40 (s, 2H), 7.22-7.91 (m, 7H); IR ($CHCl_3$) 3400, 1620, 1580, 1450 and 870 cm^{-1} .
- g. This reaction and the reaction in entry 7 were conducted by Dr. John T. Gupton and included for completeness. This product was recrystallized by an ethanol/water mixture resulting in a 53% yield after purification. NMR (d^6 -DMSO) δ 7.38-7.95 (m, 7H); IR ($CHCl_3$) 3380, 1630, 1580, 1450 and 850 cm^{-1} .
- h. NMR (d^6 -DMSO) δ 7.27-8.46 (m, 7H); IR ($CHCl_3$) 3400, 1600, 1580 and 870 cm^{-1} .

N-(2-Methoxyphenyl)-N'-(2,4-Dichlorobenzoyl)hydrazine

A 250-ml, three-necked, round-bottomed flask was equipped with a West condenser, thermometer adaptor, thermometer, stirring bar, 100-ml addition funnel and tubing leading from the condenser to a mineral oil bubbler. The flask was charged with 8.3g (0.050 mol) of 2-methoxybenzhydrazide, 4.2g (0.050 mol) of sodium bicarbonate and 60 ml each of water and THF (the relative amounts of THF and water are dependent upon the solubility of the solids in this binary system).

2,4-Dichlorobenzoylchloride was added dropwise to the flask with stirring. Since solid was not observed during the initial stages of the reaction at room temperature, the reaction mixture was warmed at 31°C

for 1 hr. during which time a solid separated. Approximately 100 ml of water was added to the flask with cooling and stirring in order to induce further crystallization. The resulting white solid was filtered, washed with cold water and dried using a vacuum pump and a Kugelrohr apparatus affording 15.3g (90% yield) of white crystalline solid having a melting point range of 155-165°C. The solid was recrystallized with a methanol-water mixture (90% recovery) and found to be insoluble in 5% hydrochloric acid solution and soluble in aqueous alkali: ¹⁷ mp 182-184°C; NMR (CDCl₃) δ 4.12 (s, 2H) and 6.93-8.05 (m, 7H); IR (CHCl₃) 3360 (N-H 2° amide stretch), 1620 (C=O amide stretch), 1450 (aromatic C=C), 1020 (aromatic ether) and 870 cm⁻¹ (2,4-disubst'd).

4. Preparation of 2,5-disubstituted-1,3,4 oxadiazoles



Table VI

Experimental Data for the Preparation of Oxadiazoles

Entry	R ₁	R ₂	Yield ^a (%)	mp (°C)	
				Crude	Recryst.
1	2,4-dichlorophenyl	phenyl	65 ^b	107-109	118-120 ²
2	2-methoxyphenyl	2,4-dichlorophenyl	65 ^b	55-59	176-179
3	3-methoxyphenyl ^c	2,4-dichlorophenyl	95	98-102	—
4	2-fluorophenyl ^d	2,4-dichlorophenyl	98	126-130	—
5	3-fluorophenyl ^e	2,4-dichlorophenyl	85	117-119	—
6	2-(trifluoromethyl)phenyl ^f	2,4-dichlorophenyl	86	65-82	—
7	3-(trifluoromethyl)phenyl ^g	2,4-dichlorophenyl	88	75-80	—

a. The yields reported refer to crude yields unless otherwise specified.

b. These reactions proceeded using excess polyphosphoric acid rather than 400 g of PPA for every 0.2 mole of diacylhydrazine. One may infer from the above data that the yield of the reaction increases as one conforms to the specified ratio² of starting materials - 400g of PPA per 0.2 mole of diacylhydrazine. These two solids were recrystallized from ethanol resulting in poor recovery (entry 1: 60%, entry 2: 15%). Entry 1: NMR (CDCl₃) δ 7.20-7.69 (m, 5H) and 7.89-8.29 (m, 3H); IR (CHCl₃) 1590, 1450, 1030, 970 and 870 cm⁻¹. Entry 2: NMR (CDCl₃) δ 4.05 (s, 3H) and 6.98-8.22 (m, 7H) IR (CHCl₃) 1590, 1450, 1020, 970 and 870 cm⁻¹.

c. NMR (d⁶-DMSO) δ 3.91 (s, 3H) and 7.37-8.25 (m, 7H); IR (CHCl₃) 1590, 1550, 1450, 1040, 970 and 870 cm⁻¹.

d. NMR (CDCl₃) δ 7.20-8.31 (m, 7H); IR (CHCl₃) 1590, 1450, 1020, 960 and 870 cm⁻¹.

- e. NMR (CDCl_3) δ 7.20-8.24 (m, 7H); IR (CHCl_3) 1590, 1450, 1040, 970 and 870 cm^{-1} .
- f. NMR ($\text{d}^6\text{-DMSO}$) δ 7.37-8.34 (m, 7H); IR (CHCl_3) 1590, 1450, 1030, 970 and 870 cm^{-1} .
- g. See experimental procedure below for spectral data.

2-(2,4-Dichlorophenyl)-5-[3-(Trifluoromethyl)phenyl]-1,3,4-Oxadiazole

The equipment for the preparation of these 1,3,4-oxadiazoles consisted of the following: a 250-ml, three-necked, round-bottomed flask, Frederick condenser, thermometer and adapter, mechanical stirrer and glass stopper. In this reaction 400 g of PPA was used for every 0.2 mole of diacylhydrazine² and the reaction was carried out on a 5.0 gram scale. To the flask was added 28g of PPA which was weighed directly into the flask in a hood. The flask was heated to about 50°C in order to decrease the viscosity of PPA at which time 5.0g (0.014 mol) of N-[3-(trifluoromethyl)benzoyl]-N'-(2,4-dichlorobenzoyl)hydrazine was added in one portion. The reaction mixture was heated with stirring for five hours at 130°C . The flask and contents were cooled to below 100°C and 105 ml of water was added to the flask (150 ml of water is added to the flask for every 40g of PPA utilized in the reaction).² This mixture was stirred for several minutes with the formation of a precipitate. The contents of the flask were poured into a beaker and cooled in an ice-water bath. The solid was filtered, washed with cold water, vacuum filtered overnight and dried @ .07 mm Hg, yielding 4.2g (88% yield) of gray solid: mp $75\text{-}80^\circ\text{C}$; NMR ($\text{d}^6\text{-DMSO}$) δ 7.39-8.51 (m, 7H); IR (CHCl_3) 1590 (C=N stretch), 1450 (aromatic C=C), 1040, 970 (C-O stretch) and 870 cm^{-1} (aromatic C-H).

III. DISCUSSION OF RESULTS

Tables I, II, III, IV, V and VI, tabulate the formamidino esters, amidines, methyl benzoates, benzhydrazides, diacylhydrazines and 2,5-disubstituted-1,3,4-oxadiazoles which were synthesized respectively in good to excellent yields. The products were characterized by NMR or IR spectroscopy.¹⁸⁻²¹ These compounds were usually produced in sufficient purity or purified by either distillation or recrystallization.

In reference to Section II-A one can see that α -formamidine-methyl esters are produced by amino acids where the acid group was converted to an ester group and the amino group was converted to a formamidine group. The structural assignment for the amidine group was based upon the presence of a C=N stretch (1640 cm^{-1}) and an N-CH₃ stretch ($2820\text{--}2760\text{ cm}^{-1}$). Also, the absence of the two 1° amine N-H stretching bands ($3500\text{--}3300\text{ cm}^{-1}$) and an N-H bending vibration ($1650\text{--}1580\text{ cm}^{-1}$) signifies that most, if not all, of the starting amino acid was converted. The infrared spectra of these formamidino esters consistently revealed a C=O stretch at 1740 cm^{-1} . All of this infrared data was consistent with the findings of Fitt and Gschwend.³ The NMR absorption at 2.8-2.9 ppm (s, 6H) was assigned to the N,N-dimethyl group while the absorption at 3.6-3.7 ppm (s, 3H) was responsible for the methyl group of the ester. Also the NMR absorption in the range 3.3-4.0 ppm and at 7.3 ppm are representative of the α -hydrogen and the formamidine hydrogen,

respectively. The chemical shift of the α -hydrogen varies depending on the type of amino acid reacted. This data was also in agreement with that reported by Fitt and Gschwend.³ These liquids must be stored in a refrigerator or freezer if appreciable deterioration is to be avoided.³

In Section II-B we noted that various amidines could be produced in good yields from their corresponding primary amine and the readily accessible, inexpensive β -dimethylamino methylenating agent "Gold's reagent". The structure of these amidines were also determined by NMR and IR spectroscopy. Likewise, as in the formamidino esters above, the IR spectra of the amidine products indicate a >C=N- stretch at 1640 cm^{-1} , a C-N stretch at $1350\text{--}70\text{ cm}^{-1}$ and when applicable an aromatic C=C stretch at $1570\text{--}1610\text{ cm}^{-1}$ and aromatic C-N stretch at 1380 cm^{-1} . Also it is suspected that mainly the trans isomer of N,N-dimethyl-N'-oleylformamidine was formed due to a trans olefin stretch at $\sim 960\text{ cm}^{-1}$ ($\text{H}-\text{C}=\text{C}-\text{H}$).

The NMR data consists mainly of two critical peaks necessary for characterization of the amidines; δ an absorption at 2.7-3.0 ppm (s, 6H) for the N,N-dimethyl group and an absorption at 7.2-7.3 ppm (s, 1H) for the formamidine hydrogen ($-\text{N}=\text{C}-\text{H}$).

The third section of Part I dealt with the synthesis of two classes of compounds, diacylhydrazines and 2,5-disubstituted-1,3,4-oxadiazoles, which may possess biological activity (see Tables V and VI). However, the synthesis of these two classes of compounds requires that one first synthesize the ester from the carboxylic acid and then convert the ester to the hydrazide. Thus, the spectroscopic data necessary for the identification of all intermediates will be discussed.

The methyl benzoates were synthesized by either an orthoamide (method A) or methyl iodide (method B). Method B proved to be the most advantageous route since the product methyl benzoate did not require distillation and was synthesized in high purity as seen by GLC. The infrared spectra reveal a strong carbonyl ester stretch at 1725 cm^{-1} while the NMR spectra reveal a singlet for three hydrogens at 3.9-4.0 ppm which is indicative of the methyl group. After conversion of the ester into the hydrazide, however, the carbonyl stretching frequency is decreased by approximately 55 cm^{-1} . There are four characteristic peaks which should be displayed in the infrared for hydrazides; a peak at $3440\text{--}3420\text{ cm}^{-1}$ for a N-H 1° amine stretch, 3320 cm^{-1} for an N-H 2° amide stretch, 1670 mc for a carbonyl amide stretch and 1620 cm^{-1} for N-H bending (1° amine). This data as well as other data was verified by various sources. Smith ¹⁷ states that the spectra of hydrazides, as in amides, reveal two bands in the "carbonyl region," at 1620 cm^{-1} and $1670\text{--}1630\text{ cm}^{-1}$. Similarly, Jensen ²² and Prevorsek ²³ cite these absorptions as well as others. Zabicky ²⁴ mentions that crystalline hydrazides reveal three amide absorptions; $1670\text{--}1625\text{ cm}^{-1}$ (carbonyl), $1570\text{--}1530\text{ cm}^{-1}$ (C-N-H vibration) and $1305\text{--}1200\text{ cm}^{-1}$. He also attributes the weak band at $1620\text{--}1610\text{ cm}^{-1}$ to NH_2 deformation and believes that the hydrazide dissolved in chloroform will result in a shifted carbonyl stretch ($1690\text{--}1645\text{ cm}^{-1}$) and C-N-H vibration (1500 cm^{-1}). A dilute solution will result in a N-H band (2° amide) at about 3450 cm^{-1} and as the concentration of the solution is increased, a band gradually appears at 3340 cm^{-1} , which was observed experimentally. This absorption is

probably due to the formation of intermolecular hydrogen bonds in concentrated solutions.²⁴ Also the hydrazides usually display a broad singlet ($\sim 3.80\text{--}4.75$) for two hydrogens ($-\text{NH}_2$) in the NMR spectra. In addition to hydrazides, diacylhydrazines exhibit an N-H 2° amide stretch which occurs at $3360\text{--}3340\text{ cm}^{-1}$ and a carbonyl amide stretch which occurs at about 50 cm^{-1} lower than that of the hydrazides (1670 cm^{-1}). Also the diacylhydrazines are characterized by the absence of a broad singlet (2H for NH_2) in the spectrum.

NMR and IR spectroscopy was also utilized in the characterization of the 2,5-disubstituted-1,3,4-oxadiazoles synthesized herein. Katritsky and Boulton²⁵ cite infrared bands at 970 and $1030\text{--}1020\text{ cm}^{-1}$ characteristic of the C-O bond and a band at $1640\text{--}1560\text{ cm}^{-1}$ which is characteristic of the C=N valence vibration. In addition, Sauer and coworkers²⁶ reveal infrared data for highly conjugated systems involving two or more 1,3,4-oxadiazole rings. They observed two prominent peaks at about 1440 and 1570 cm^{-1} . All of the above bands were noticed in the IR spectra of the oxadiazoles, the C=N stretch usually occurring at 1590 cm^{-1} . Other sources^{27, 28} reveal infrared data for 1,2,4-oxadiazoles which are very consistent with 1,3,4-oxadiazoles. One should note that some compounds in Section II-C require supersaturation in chloroform in order to obtain the IR spectrum.

When investigating the NMR spectra of methyl 2-methoxybenzoate and methyl 3-methoxybenzoate with their hydrazides, diacylhydrazines and oxadiazoles it was noted that the chemical shift of the methoxy hydrogens gradually increased when going from step I to step IV in

Figure 3. This observation may be attributed to the fact that the methoxy hydrogens become more deshielded through conjugation and electronic effects, and therefore, require less magnetic energy to alter the spin state of the protons.

IV CONCLUSIONS

Four classes of compounds (Figure 4) were synthesized in the investigation of potential insecticides with greater biological activity than those existing today. These classes of compounds include α -formamidine methyl esters (8), amidines (9), diacylhydrazines (10) and 2,5-disubstituted-1,3,4-oxadiazoles (11) and were characterized via NMR and infrared spectroscopy.

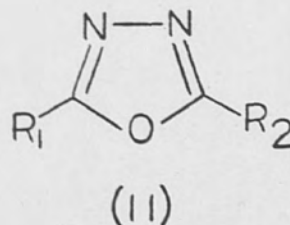
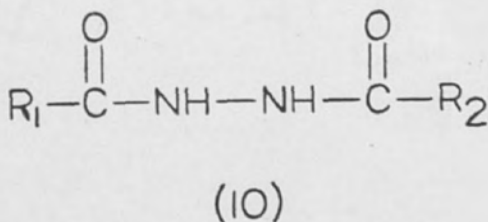
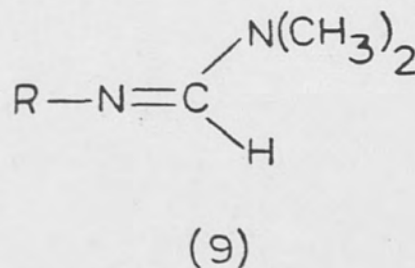
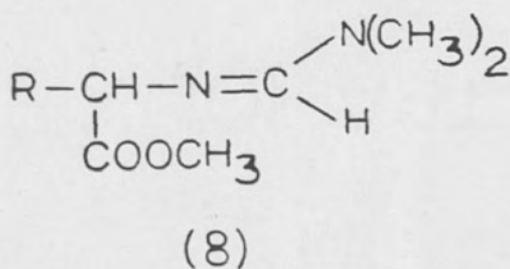


Figure 4. Classes of compounds synthesized as potential insecticides.

All of the twenty-six potential insecticides were synthesized in good to excellent yields usually under mild conditions. Therefore, they may be produced on an industrial scale and remain economically feasible in the event any of the compounds prove to be very active. The amidine in entry 4 of Table II will not be assayed for biological activity due to uncertainty in the actual structure of the solid obtained. Finally, these potential insecticides were submitted to the Agricultural Division of DOW Chemical Company for biological screening.

V. RECOMMENDATIONS

The following is an outline of some suggestions for future research.

1. Before any of the reactions in Section A, B and C are used industrially one should perform complete optimization of the reaction conditions which include time, temperature, pressure, solvent system and reactant ratios.

2. When the reactant ratio of DMFA to α -amino acid (Section A) is 3.5 to 1.0 and a slurry or solution will not develop, one should add DMF to the flask rather than additional DMFA because of the high cost of DMFA and the simultaneous recovery of DMF (solvent) with the byproduct DMF.

3. Additional formamidine analogs related to the pyrethroids may be synthesized and tested for biological activity as well as additional heterocyclic and fatty acid type amidines (Section B).

4. For the preparation of hydrazides from their corresponding methyl benzoates (Table IV) one should test dimethoxyethane as the solvent rather than methanol. Since methanol is a byproduct of the reaction, it is suspected that dimethoxyethane may affect the thermodynamics by shifting the equilibrium further toward the product side. Also the increase in the boiling point (65°C to 85°C) may drive the reaction further to completion and increase the yield.

5. As one can see from Table V for the preparation of diacylhydrazines, the reaction temperature varied for different reactions, and thus, should be one of the first variables optimized in the reaction.

6. For the preparation of 2,5-disubstituted-1,3,4-oxadiazoles one should adhere to the specified reactant ratio of grams of PPA per mole of diacylhydrazine since the yield was found to decrease as the number of grams of PPA was increased.

Also, due to the high viscosity of PPA, one should weigh the PPA directly into the reaction vessel by carefully and gradually pouring the PPA directly into the flask.

PART II

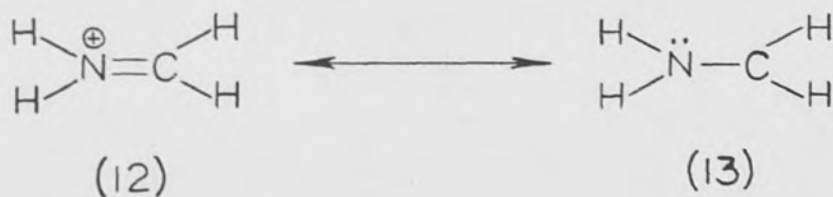
NEW SYNTHETIC APPLICATIONS OF VINAMIDINIUM
AND AZAVINAMIDINIUM SALTS:

REACTIONS WITH REDUCING AGENTS
AND NITRO COMPOUNDS

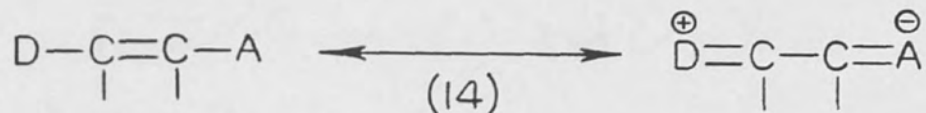
I. INTRODUCTION

Considerable interest has recently been displayed concerning the preparation^{29,30} and synthetic utility³¹⁻³⁴ of preformed iminium salts, however, little investigative work has been pursued using the novel iminium salt [3-(dimethylamino)-2-azaprop-2-en-1-ylidene] dimethylammionium chloride (Gold's reagent) or arylvinamidinium salts. Due to the suspected synthetic and industrial utility, this area of chemistry will be investigated further. A general introduction to this type of chemistry as well as the basis for pursuing this area of research will follow.

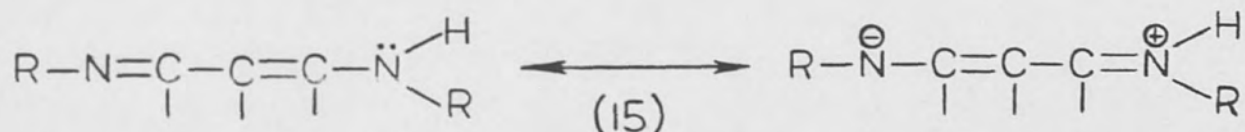
The structure of a simple iminium ion, CH_2NH_2^+ , is described³⁵ by two resonance structures (12) and (13). However, when an amino group is bonded to the carbon atom, an amidine system is said to exist. This



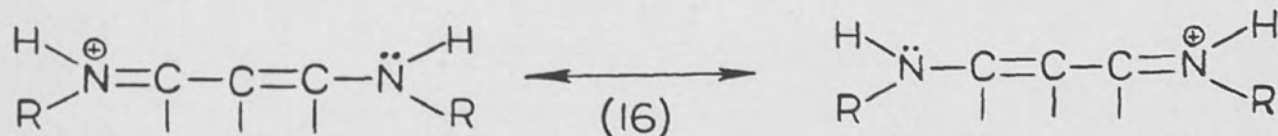
system may also be referred to as a "push-pull" alkene system. For a "push-pull" alkene system to exist it must have an electron-donating group (D) attached to one end of the double bond and an electron-withdrawing group (A) attached to the other end. This system is illustrated below (14).



The above push-pull alkene maintains enhanced stability relative to other alkenes due to delocalization of electrons from the donor group through the double bond to the acceptor group. If one slightly increases the size of the molecule and the electron donor group is an amino group then a vinamidine system (15) may result. This system has been called a vinamidine system because it represents a vinylog of an



amidine.³¹ Similarly, a vinamidinium salt (16) may exist where we have a charged species with its counter ion rather than a neutral species. Vinamidinium salts are most interesting due to their symmetrical nature



and enhanced stability through delocalization of six pi electrons and charge transfer. Usually ininium salts and vinamidinium salts are solids and sometimes easily hydrolyzed on contact with moisture. Vinamidinium salts or "push-pull" alkenes have been shown to react with both electrophiles and nucleophiles, and tend to undergo substitution rather than addition reactions due to their enhanced stability. Their α and β carbon atoms are, respectively, electrophilic and nucleophilic, and therefore, react with nucleophiles and electrophiles, respectively, to form σ complexes. These intermediate σ complexes lose a group thereby yielding a substitution product.³² These reactions are delineated in Figure 5.

The preparative value of vinamidinium salts has already been described in the literature. They react with nucleophiles to form pyrazoles, oxazoles, pyrimidines, diazepines, quinolines, quinolizines, phenanthrenes, carbazoles, benzofurans, indoles and other compounds.

With this background information let us now consider the specific chemistry that will be investigated. In 1960 Gold^{37,38} described the preparation of a novel iminium or azavinamidinium salt, [3-(dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride (17), which will be referred to as "Gold's reagent". The synthetic applications and mode of reaction of Gold's Reagent are now being pursued more extensively by Gupton^{8,39-41} and coworkers. Gold's reagent was synthesized using the readily available starting materials cyanuric chloride and N,N-dimethylformamide (DMF) as outlined below (Figure 6). The mechanism for this preparation has been proposed by Gold.^{37,42}

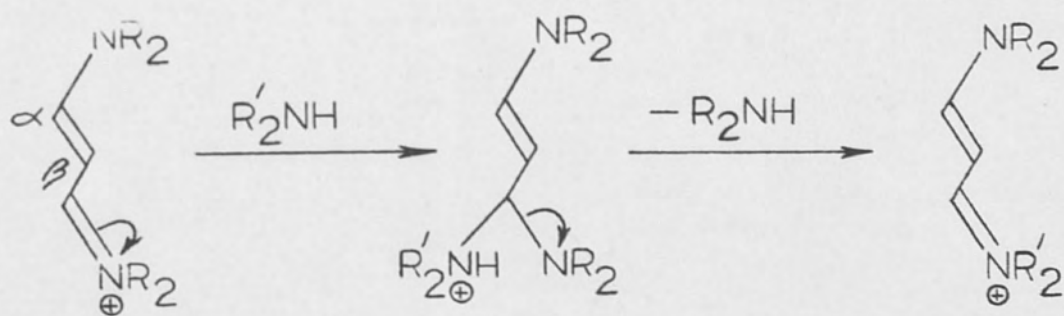
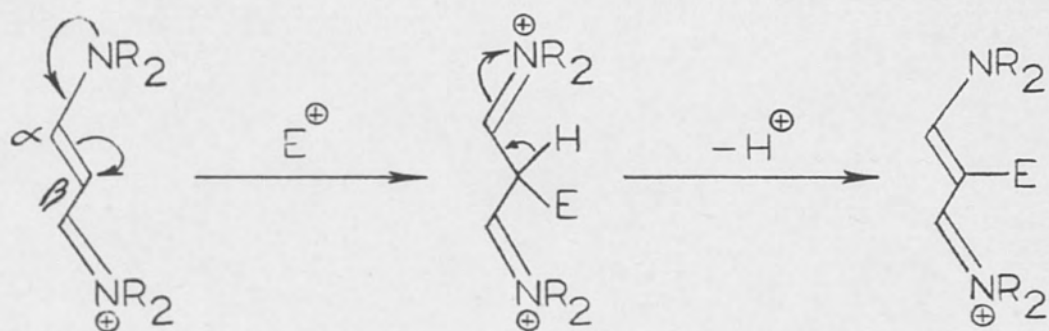


Figure 5. Reaction of vinyliminium salts with electrophiles and nucleophiles.

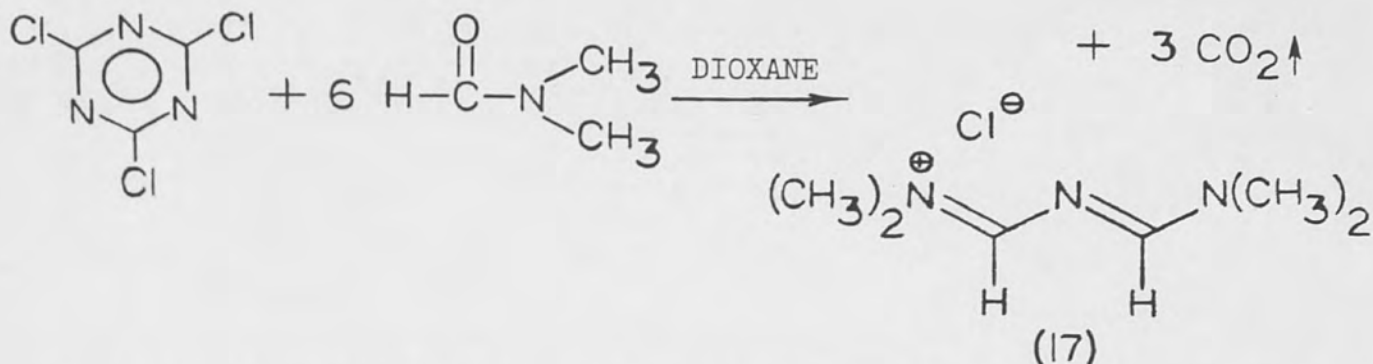


Figure 6. Preparation of Gold's reagent from cyanuric chloride and DMF.

As illustrated in Figure 6, Gold's reagent is prepared from inexpensive materials and therefore may be obtained readily on an industrial scale in the event its reaction products are synthetically or commercially useful. There are three possible geometric isomers³⁶ with which vinamidinium salts may exist; however, Gold's reagent was found to exist in an all trans ('W') configuration (17). This was found by x-ray diffraction and was consistent with its ¹H-NMR spectrum (CDCl₃).⁴²

It has recently been found that Gold's reagent (17) produces products identical with those obtained from DMFA and in higher yields. Thus, the basis for continued interest in this azavinamidinium salt is the fact that Gold's reagent has chemical and economic advantages over the formamide acetals. The formamide acetals are expensive, moisture and heat sensitive, require potent, mutagenic alkylating agents for their preparation, require high reaction temperatures and sometimes require longer reaction times. On the other hand, Gold's reagent is prepared in quantitative yield in one step from inexpensive raw materials, and requires no special purification process. Although

Gold's reagent is moisture sensitive, it has already proven to be a promising β -dimethylamino methylenating agent,⁸ and therefore will be investigated with other nucleophiles.

In a review article by R.F. Abdulla and R.S. Brinkmeyer⁴³ entitled "The Chemistry of Formamide Acetals," it was shown that substituted toluenes could react with formamide acetals to form enamines in generally good yields (Figure 7). The basis for this reaction is

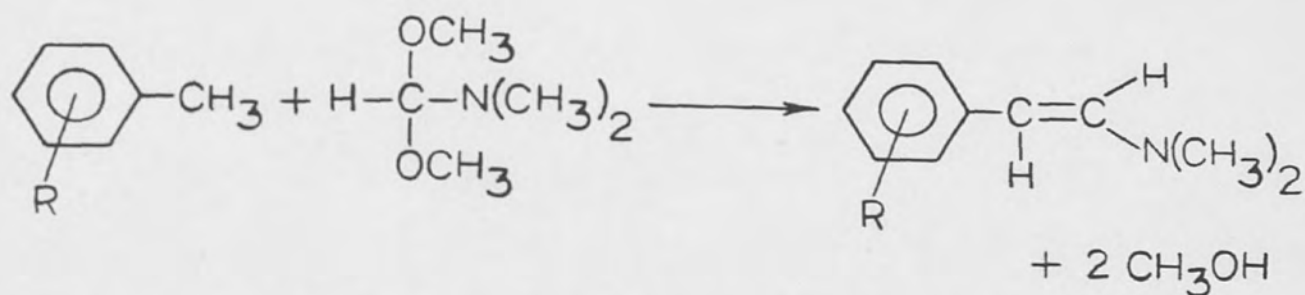
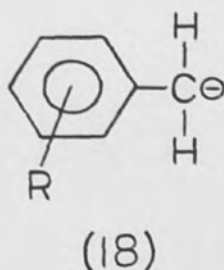


Figure 7. Preparation of enamines via DMFA and substituted toluenes.

probably generation of an activated methylene intermediate (18) which then combines with the formamide acetal carbonium ion intermediate. Also, it was found by Nair and Cooper^{44,45} that one may selectively alkylate methylene compounds (enolates of ketones, esters and lactones) via vinamidinium salts to yield dienaminones. The dienaminones and



dienamines⁴⁵ prepared by Nair and Cooper are multifunctional and are potentially useful in the synthesis of some natural products. As a result, it is the purpose of the investigator to examine the use of Gold's reagent as a more effective and economical formylating agent relative to the formamide acetals. The reaction of Gold's reagent with nitromethane and p-nitrotoluene will be investigated where the p-nitrotoluene reaction conditions will be optimized with regard to solvent, base and temperature. Other chemists have reacted o-nitrotoluene and p-nitrotoluene with formamide acetals to form the corresponding enamine in 47% and 73% yield, respectively.^{46,47}

Furthermore, as a result of the recent success in investigating the chemistry and utility of vinamidinium salts, a further objective of the investigator is to prepare a series of substituted arylvinamidinium salts (19) and examine their reaction with various reducing agents in hopes of obtaining synthetically important intermediates. The preparation of these arylvinamidinium salts is discussed in various articles⁴⁸⁻⁵⁰ and occurs via readily accessible starting materials. The mechanism for this reaction occurs through a Vilsmeier-Haack type intermediate⁵¹ where an iminium salt is generated by reacting DMF with phosphoroylchloride. The overall balanced reaction after addition of sodium perchlorate to the crude reaction mixture is outlined in Figure 8.

Over the years, organic chemists have shown interest in the reduction of iminium salts. Recently, Nilsson⁵² and Sundberg⁵³ have made advances in this area of research. Nilsson found that the

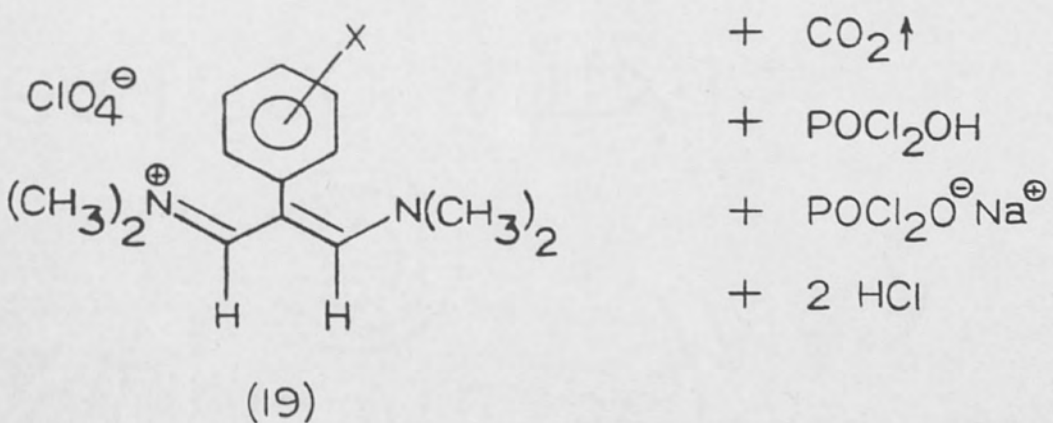


Figure 8. Preparation of arylvinamidinium perchlorates from carboxylic acids and DMF.

protonated form of enaminones undergoes selective reduction to give α, β -unsaturated ketones (20), which are formed by deamination of the initially produced amino ketone (Figure 9). In comparison, Sundberg has shown (Figure 10) that thioenaminones can be selectively methylated on sulfur to produce an iminium salt which in turn may be selectively reduced to yield vinyl sulfides (21). As a result of the above accounts, our ⁵⁴continuing interest in the chemistry of iminium salts, and the potential applications of the reaction products, the reduction of a series of 2-arylvinamidinium perchlorates will be investigated using sodium borohydride and sodium cyanoborohydride. Both sodium borohydride and cyanoborohydride have been heavily studied⁵⁵⁻⁵⁶ for reducing the iminium ion. The reaction products will be characterized and their respective yields obtained. These vinamidinium salts (19) were chosen for this study because of their accessibility⁴⁸⁻⁵⁰ from the corresponding phenylacetic acids.

In addition to examining sodium borohydride and sodium cyanoborohydride as potential reducing agents of the vinamidinium moiety, additional reducing agents will be examined in order to understand the scope of the reduction of vinamidinium salts.

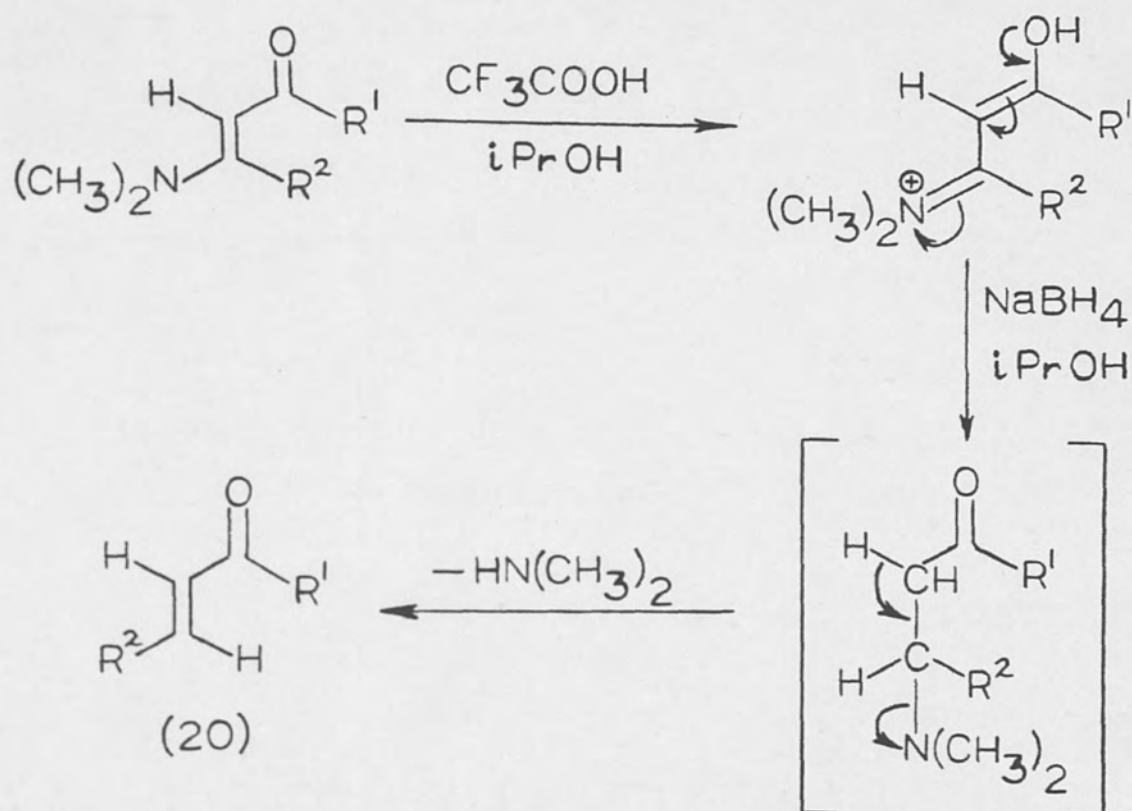


Figure 9. Preparation of α,β -unsaturated ketones from enaminones via selective reduction using sodium borohydride.

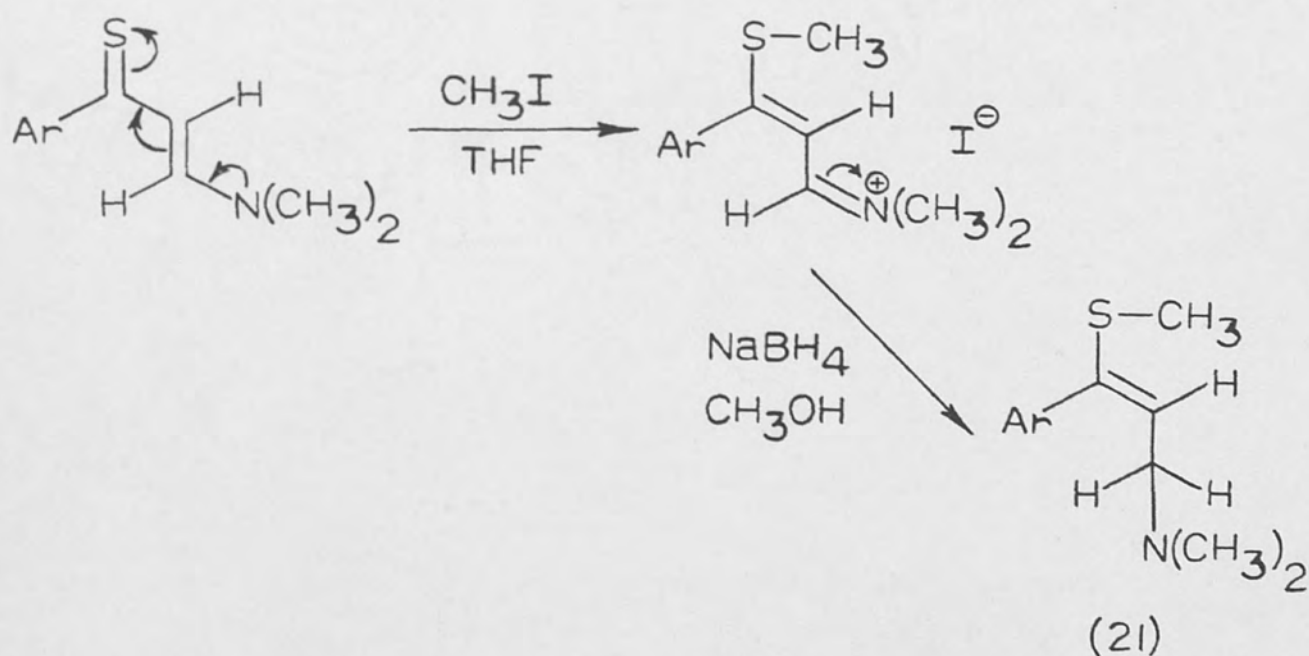


Figure 10. Preparation of vinyl sulfides from thioenaminones via selective reduction using sodium borohydride.

II. EXPERIMENTAL

A. Preparation of Nitroenamines via "Gold's Reagent"

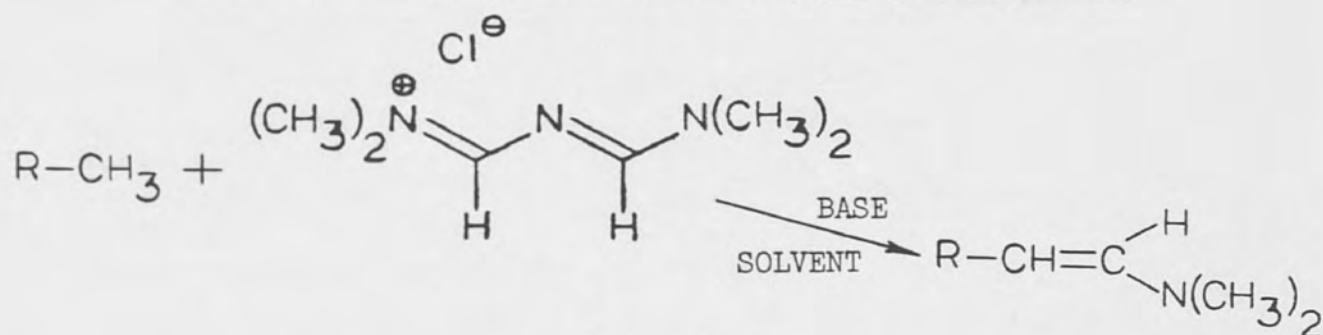


Table VII

Optimization of Reaction Conditions for the Synthesis of Nitroenamines

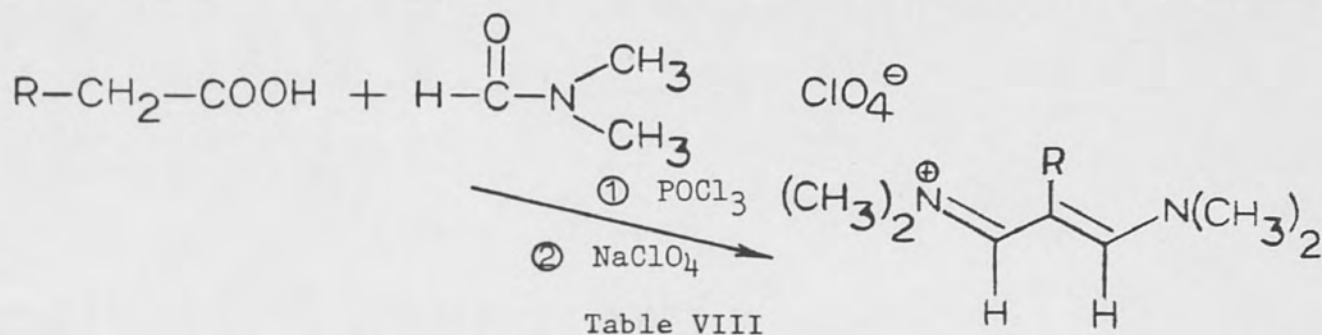
Entry	R	Solvent	Base	Temp (°C)	Time
1	nitro ^a	MeOH	NaOMe	65 (reflux)	24
2	p-nitrophenyl ^b	MeOH	NaOMe	65 (reflux)	24
3	p-nitrophenyl ^b	i-PrOH	NaOi-Pr	82 (reflux)	24
4	p-nitrophenyl ^a	t-BuOH	NaOt-Bu	118 (reflux)	24
5	p-nitrophenyl ^a	DMF	NaH	25 (rt)	72
6	p-nitrophenyl ^a	cyclohexanol	NaO-C ₆ H ₁₁	160 (reflux)	24
7	p-nitrophenyl ^c	ET ₃ N (THF)	NaH	75 (reflux)	24

- a. No sign of the desired reaction occurred as seen by NMR spectroscopy.
- b. The reactions occurred to a limited extent (entry 2: 30-40% yield; entry 3: 50-55% yield).
- c. This reaction occurred three times; once with a 10% excess of Gold's reagent, once with a 30% excess of NaH and 50% excess of Gold's Reagent and once with a 50% excess of NaH and 100% excess of Gold's reagent. The most favorable results were obtained using 30% excess NaH and 50% excess Gold's Reagent (50% conversion and 90% yield).


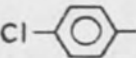
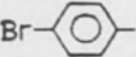
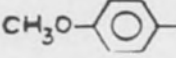
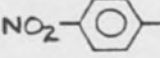
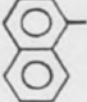
E- β -Dimethylamino-4-Nitrostyrene

A 250 ml, three-necked, round-bottomed flask was equipped with a thermometer adapter, thermometer, reflux condenser, stirring bar, nitrogen line and an addition funnel. A solution containing 6.8g (0.050 mol) of p-nitrotoluene in 25 ml of THF was added dropwise at room temperature to the flask containing 3.1g (0.065 mol) of sodium hydride (50% by weight mineral oil) in 75 ml of triethylamine. Hexane was used to remove the mineral oil from sodium hydride prior to reaction and a nitrogen atmosphere was maintained at all times. The solution was stirred for several minutes upon which 12.3g (0.075 mol) of Gold's reagent (17) was added in one portion. The reaction continued while refluxing (75°C) with stirring overnight. Upon completion of the reaction, 10 ml of isopropanol was added to the flask. The volatiles (THF, Et_3N , iPrOH) were then removed in vacuo using a rotating evaporator, and the residue was taken up in 100 ml of chloroform. The organic phase was extracted twice with one 150 ml portion of an unsaturated sodium bicarbonate solution. The chloroform phase was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford a dark brown semisolid. The starting material was distilled (Kugelrohr) at 50-78°C and 0.4 mm Hg giving rise to a gummy residue. The residue was recrystallized with a hexane-chloroform solution, resulting in 4.4g (73% yield) of dark crystalline solid: mp 104-112°C (lit.⁴⁷ mp 137-139°C); NMR (CDCl_3) δ 2.92 (s, 6H), 4.99-5.40 (d, $J=13\text{Hz}$, 1H), 6.88-7.15 (d, $J=13\text{Hz}$, 1H), 7.03-7.31 (m, 3H) and 7.92-8.15 (d, 2H); IR (CHCl_3) 1630, 1580 (aromatic C=C), 1500 and 1330 cm^{-1} (NO_2).

B. Preparation of Arylvinamidinium Salts from Substituted Acetic Acids



Experimental Data for the Preparation of Arylvinamidinium Perchlorates

Entry	R	Yield ^a (%)	lit. mp (°C)
1		99 ^b	193-194 ⁴⁹ 200-201 ⁵⁰
2		88	142-144 ⁴⁹
3		73 ^c	152-154 ⁴⁹
4		82	130-131 ⁴⁹
5		99	225-226 ⁵⁰
6		83 ^d	195-196 ⁴⁹ 203-204 ⁵⁰

- a. The yields reported refer to crude yields unless otherwise specified.
- b. See reference 57 for NMR data.
- c. This yield is lower than expected due to the discovery of an error in the initial calculations; it was discovered that less than a 1:1 ratio of sodium perchlorate to p-bromophenylacetic acid was utilized in the reaction.
- d. This yield refers to the yield after recrystallization from isopropanol. The crude material maintained a mp = 186-192°C. See the experimental procedure for the experimental details using naphthylacetic acid.

α -Naphthyltrimethinium Perchlorate

To a 250 ml, three-necked, round-bottomed flask was added 36.5g (0.50 mol) of DMF and 28 ml (0.30 mol) of phosphorus oxychloride. The solution was stirred using a mechanical stirrer and cooled with an ice bath while 18.6g (0.10 mol) of α -naphthylacetic acid was added in several portions. The flask was equipped with a thermometer and adapter, condenser and mineral oil bubbler. The solution was stirred for three hours while controlling the pot temperature at 90°C. The reaction was exothermic and upon completion of carbon dioxide evolution, a drying tube was connected to the condenser. The reaction mixture was cooled via an ice bath and added to 100 g of ice-water. The solution was stirred with a small amount of Norite and filtered after a mobile solution was obtained. A precipitate was produced when 21.4g (0.175 mol) of sodium perchlorate was added to the filtrate with stirring and cooling in an ice bath. The vinamidinium salt was filtered, washed with sodium perchlorate solution and dried affording a brown solid having a mp = 186-192°C. The solid was recrystallized from isopropanol resulting in 29.3g (83% yield) of crystalline solid: mp 197-200°C; NMR (CDCl₃) δ 2.24 (s, 6H), 3.35 (s, 6H), 7.33-8.02 (m, 7H) and 8.07 (s, 2H); IR (CHCl₃) 1590 (C=N stretch), 1400 (N-CH₃) and 1290 cm⁻¹ (aromatic C=C).

C. Reduction of Arylvinamidinium Perchlorates

1. Reduction of arylvinamidinium perchlorates using sodium borohydride.

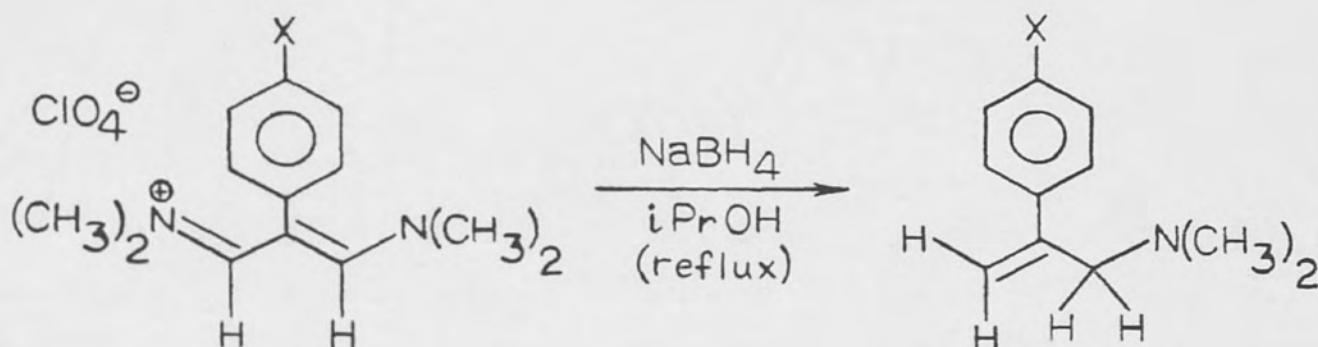


Table IX

Experimental Data for the Preparation of N,N-Dimethylallylic Amines

Entry	X	% Yield ^a	bp (°C)
1	H ^b	72	55-60 (.4mm)
2	Cl ^c	68	60-65 (.2mm)
3	OCH ₃ ^d	79	73-79 (.3mm)
4	NO ₂ ^e	55	105-118 (.5mm)

- All yields refer to distilled products. Compounds in entries 1-3 were found to be greater than 95% pure as determined by glc analysis on a 6' x 1/4", SE-30 column (program 150-200°C at 20°C/min.). The nitro compound (entry 4) was found to be greater than 85% pure under the same conditions of analysis.
- NMR (CDCl₃) δ 2.11 (s, 6H), 3.18 (broad s, 2H), 5.15 (d, J=1Hz, 1H), 5.38 (d, J=1Hz, 1H) and 7.18-7.60 (m, 5H); IR (thin film) 3080, 3050, 3020, 2810, 2760, 1620, 900, 775 and 700 cm⁻¹; mass spectrum m/e 161 (M⁺).

- c. NMR (CDCl_3) δ 2.14 (s, 6H), 3.17 (broad s, 2H), 5.15 (d, $J=1\text{Hz}$, 1H), 5.34 (d, $J=1\text{Hz}$, 1H), 7.18 (d, $J=8\text{Hz}$, 2H) and 7.40 (d, $J=8\text{Hz}$, 2H); IR (thin film) 3080, 3015, 2810, 2760, 1610, 910 and 830 cm^{-1} ; mass spectrum m/e 195 (M^+) and 197 (M^+).
- d. See the experimental procedure below for the spectral data.
- e. NMR (CDCl_3) δ 2.11 (s, 6H), 3.20 (broad s, 2H), 5.30 (broad s, 1H), 5.50 (broad s, 1H), 7.56 (d, $J=8\text{ Hz}$, 2H) and 8.00 (d, $J=8\text{Hz}$, 2H); IR (thin film) 3080, 2810, 2760, 1620, 1510, 1340, 920 and 850 cm^{-1} ; mass spectrum m/e 206 (M^+).

2-(p-Methoxyphenyl)-3-N,N-Dimethylamino-1-Propene

A round bottomed flask was equipped with a magnetic stirrer, condenser and drying tube. Into the flask was placed 1.4g (0.036 mol) of sodium borohydride and 100 ml of isopropanol. The mixture was stirred for several minutes and 6.0g (0.018 mol) of entry 3 above ($X=\text{OCH}_3$) was added in one portion. The resulting mixture was refluxed with stirring overnight. After the mixture was cooled to room temperature, the solvent was removed in vacuo and the residue was partitioned between chloroform (3 x 50 ml) and water (50 ml) and the combined chloroform extracts were dried over anhydrous sodium sulfate. The drying agent was removed and the solution concentrated in vacuo to leave 3.6g of a reddish oil. This material was distilled (Kugelrohr) to yield 2.7g (79% yield) of a colorless liquid: bp $73-79^\circ\text{C}$ (0.3 mm); NMR (CDCl_3) δ 2.12 (s, 6H), 3.12 (broad s, 2H), 3.60 (s, 3H), 5.08 (d, $J=1\text{Hz}$, 1H), 5.30 (d, $J=1\text{Hz}$, 1H), 6.72 (d, $J=8\text{ Hz}$, 2H) and 7.40 (d, $J=8\text{Hz}$, 2H); IR (thin film) 3080, 3015, 2810, 2760, 1470, 890 and 830 cm^{-1} ; mass spectrum m/e 191 (M^+).

2. Reduction of arylvinamidinium perchlorates using sodium cyanoborohydride

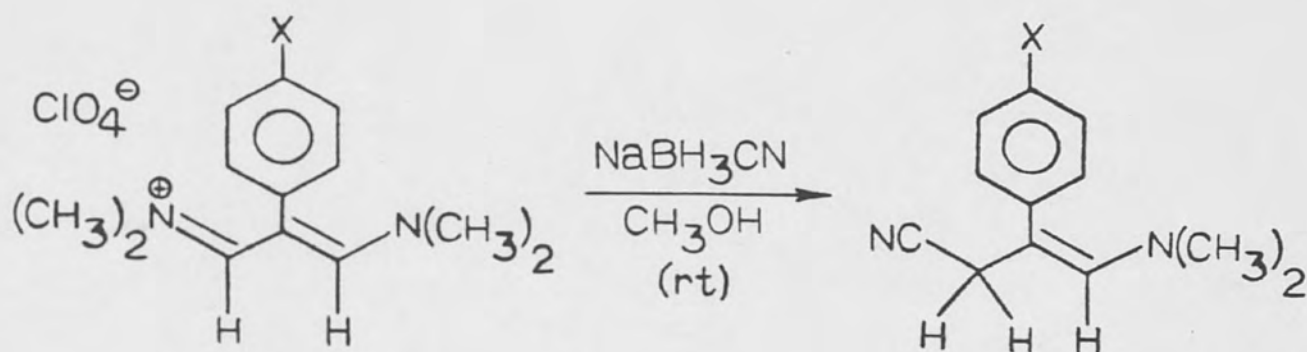


Table X

Experimental Data for the Preparation of 3-Cyanoenamines

Entry	X	% Yield ^a	bp (°C)
1	H ^b	68	100-105 (.08mm)
2	Cl ^c	72	80-150 (.08mm)
3	OCH ₃ ^d	74	109-118 (.08mm)
4	NO ₂ ^e	59	145-150 (.09mm)

a. All yields refer to compounds purified by column chromatography on Millincrodt SilicAR CC-7, 100-200 mesh silica gel. Compounds in entries 1, 2 and 4 were found to be greater than 95% as determined by glc analysis on a 6' x 1/4" SE-30 column (isothermal 200°C). The methoxy compound (entry 3) was found to be 88% pure under the same conditions of analysis. The yields in entries 1 and 3 were based on recovered starting material.

b. NMR (CDCl₃) δ 2.10 (s, 6H), 3.10 (d, J=2 Hz, 2H), 5.63 (t, J=2Hz, 1H) and 7.15-7.50 (m, 5H); IR (thin film) 2820, 2770, 2220, 1615, 860, 755 and 700 cm⁻¹; mass spectrum m/e 186 (M⁺).

- c. NMR (CDCl_3) δ 2.10 (s, 6H), 3.10 (d, $J=2\text{Hz}$, 2H), 5.74 (t, $J=2\text{Hz}$, 1H), 7.30 (d, $J=8\text{ Hz}$, 2H) and 7.47 (d, $J=8\text{ Hz}$, 2H); IR (thin film) 2820, 2770, 2220, 1610, 1090, 860, 835 and 760 cm^{-1} ; mass spectrum m/e 220 (M^+) and 222 (M^+).
- d. NMR (CDCl_3) δ 2.12 (s, 6H), 3.23 (d, $J=2\text{Hz}$, 2H), 3.78 (s, 3H), 5.68 (t, $J=2\text{Hz}$, 1H), 6.90 (d, $J=8\text{ Hz}$, 2H) and 7.52 (d, $J=8\text{ Hz}$, 2H); IR (thin film) 2820, 2770, 2210, 1600, 1250, 1030, 860, 810 and 750 cm^{-1} ; mass spectrum m/e 216 (M^+).
- e. See the experimental procedure below for the spectral data.

3-Cyano-2-(p-Nitrophenyl)-1-N,N-Dimethylamino-1-Propene

A round bottomed flask was equipped with a magnetic stirrer, condenser and drying tube. Into the flask was placed 7.0g (0.02 mol) of entry 4 above ($X-\text{NO}_2$), 1.9g (0.03 mol) of sodium cyanoborohydride, and 100 ml of absolute methanol. The mixture was then stirred for 48 hr. at room temperature. The methanol was removed in vacuo and the residue was partitioned between chloroform (75 ml) and water (50 ml). The aqueous phase was extracted with additional chloroform (2 x 75 ml) and the combined chloroform extracts were dried over anhydrous magnesium sulfate. The drying agent was removed and the solution was concentrated in vacuo to leave 4.7g of a dark oil. This material was placed on a column of 150g of chloroform-washed silica gel and the column was eluted with 100% chloroform. The first 325 ml of eluant were collected and discarded. The next 205 ml of eluant, contained a dark bank and this material was concentrated in vacuo to give 2.7g (59% yield) of a dark oil; bp $145-150^\circ\text{C}$ (0.09mm); NMR (CDCl_3) δ 2.26 (s, 6H), 3.40 (broad s, 2H), 5.98 (broad s, 1H), 7.75 (d, $J=8\text{ Hz}$, 2H) and 8.27 (d, $J=8\text{ Hz}$, 2H); IR (thin film) 2820, 2775, 2220, 1595, 1520, 1350, 870, 855, 750 and 700 cm^{-1} ; mass spectrum m/e 231 (M^+). Further elution of the column with chloroform resulted in 0.7g of the nitro substituted N,N-dimethylallylic amine (entry 4, Table IX).

III. DISCUSSION OF RESULTS

As one can see from the Experimental section the reaction of p-nitrotoluene with Gold's reagent was optimized to a certain extent (Table VII), that is, about a 50% conversion and a 90% yield was obtained. NMR spectroscopy was employed to monitor the extent of the reaction by the appearance of the N,N-dimethylamino peak at 2.9 ppm and the disappearance of the methyl peak (2.5 ppm) in the starting material. The relative sizes of these peaks gave information concerning the conversion of p-nitrotoluene to its nitroenamine. Also two doublets (5.2 and 7.0 ppm) were present in the NMR spectrum which signified the desired product. Additional work should be conducted in the optimization of the reaction conditions with regard to solvent, base, temperature and time. Other reaction conditions are proposed in the recommendation section of this report.

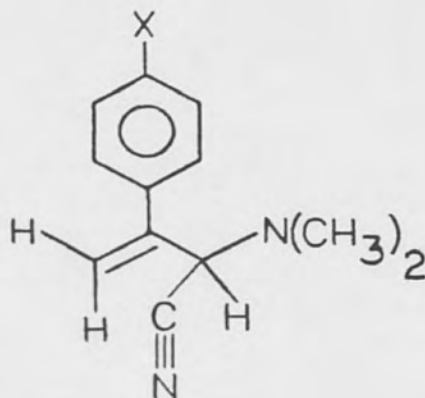
In addition, a series of arylvinamidinium perchlorates were prepared and characterized by NMR and IR spectroscopy. The NMR spectrum consistently revealed a singlet at 2.24 ppm and 3.35 ppm which were each characteristic of six dimethylamino hydrogens. Also a singlet continually appeared at 7.8 ppm due to the two "vinylic-like" hydrogens on the vinamidinium backbone. Upon synthesis of these vinamidinium salts four of the six salts were reduced with sodium borohydride (Table IX) and sodium cyanoborohydride (Table X), respectively. Reduction of these salts using sodium borohydride produced N,N-dimethylallylic amines

while reduction using sodium cyanoborohydride produced 3-cyanoenamines.

The structural assignment of the N,N-dimethylallylic moiety for the sodium borohydride reduction product was based upon the presence of aliphatic N,N-dimethyl absorptions (2810 and 2760 cm^{-1}) and a vinylic methylene absorption (900 cm^{-1}) in the infrared region. The NMR absorption at 2.1 ppm (s, 6H) was assigned to the N,N-dimethyl group and was consistent with the values reported by Sundberg⁵³ for analogous compounds. The NMR absorption at 3.0 ppm (s, 2H) was responsible for the allylic methylene group and was also consistent with Sundberg's data. Finally, the doublets ($J=1\text{ Hz}$) at 5.2 (1H) and 5.4 ppm (1H) were representative of the vinylic methylene hydrogens ($>\text{C}=\text{CH}_2$).

Upon completion of the sodium borohydride reduction reactions the vinamidinium salts were reduced with sodium cyanoborohydride to form 3-cyanoenamines. The structural identification of the 2-aryl-3-cyanoenamines in the infrared region was based upon the presence of N,N-dimethyl absorptions (2820 and 2770 cm^{-1}) and a strong cyano absorption at 2220 cm^{-1} . The NMR absorption at 2.1 ppm (s, 6H) was indicative of the dimethylamino group while the absorption at 3.1 ppm (d, $J=2\text{ Hz}$, 2H) was indicative of the 3-cyanomethylene group. The triplet at 5.7 ppm ($J=2\text{ Hz}$, 1H) was allylicly coupled to the 3-cyanomethylene group and was, therefore, assigned to the vinylic enamine hydrogen. The following structure (22) is conceivable, however, it was eliminated as a possible structure for the sodium cyanoborohydride reaction product due to the lack of vinylic methylene doublets in the NMR spectrum (5.2 and 5.4 ppm) and the lack of a vinylic methylene

absorption in the infrared (900 cm^{-1}) which were consistent with the sodium borohydride reduction products.



(22)

The pathway for the formation of the products obtained by sodium borohydride and sodium cyanoborohydride reduction of the vinamidinium salts is unique in contrast to the findings of Gupton and Polaski³⁹ concerning the addition of organometallic reagents to such electrophiles. A plausible mechanism for the formation of the allylic amines upon sodium borohydride reduction involves nucleophilic attack (addition) of a hydride ion thereby generating a product which complexes with borane (Figure 11). This complex then undergoes elimination followed by addition of another hydride ion.

In comparison, one may extrapolate this pathway (Figure 11) to the sodium cyanoborohydride reduction in order to explain the formation of the 3-cyanoenamines. Steps 1 through 3 in Figure 11 are the same for both the sodium borohydride and sodium cyanoborohydride reduction, however, step 4 is different in that anion (24) transfers hydride to the

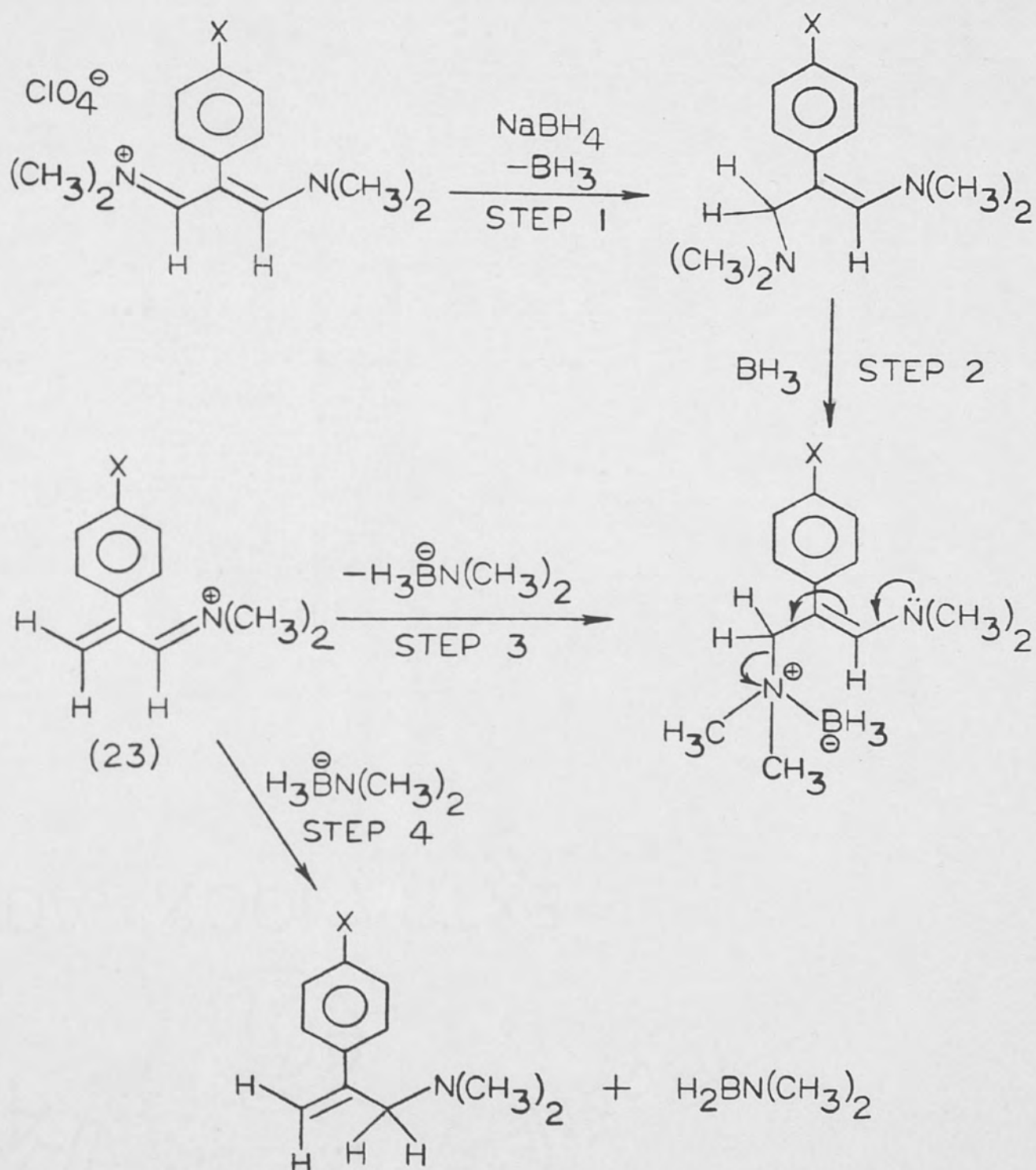


Figure 11. Proposed mechanism for the formation of N,N-dimethylallylic amines from sodium borohydride reduction of arylvinamidinium salts.

1-position of the α,β -unsaturated iminium ion (23) and anoin (26) transfer cyanide to the 3-position of the α,β -unsaturated iminium ion (Figure 12). The fact that cyanide ion undergoes nucleophilic addition

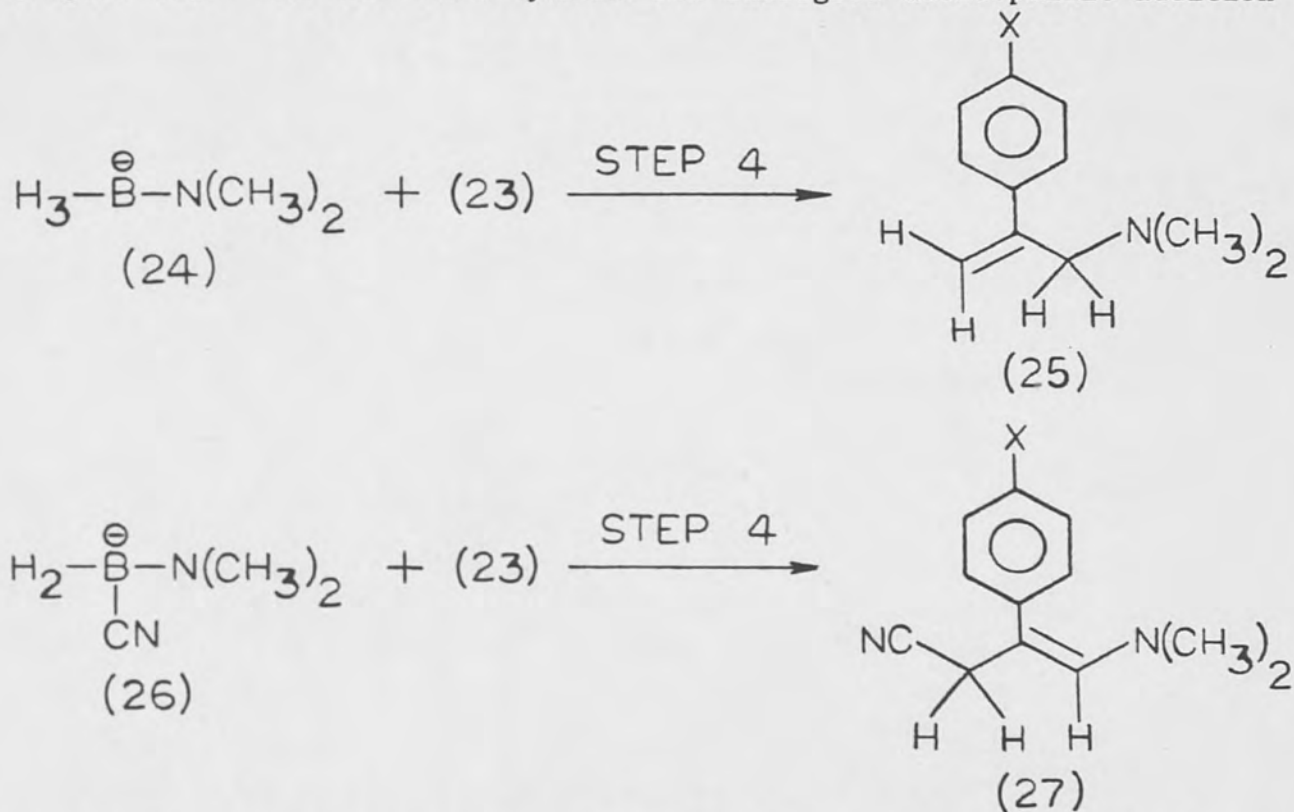
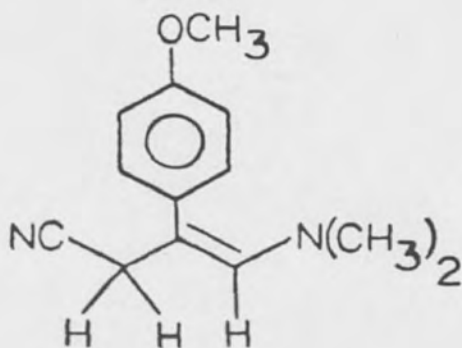


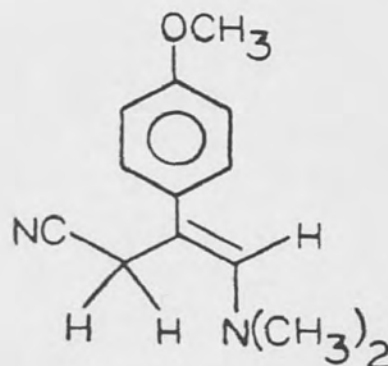
Figure 12. Step 4 in the mechanism for the reduction of vinamidinium salts with sodium borohydride and sodium cyanoborohydride.

at the 3-position as opposed to the 1-position is consistent with the reported results where addition of cyanide to α,β -unsaturated ketones was found to occur at the 3-position.⁵⁸ It was also found by GLC and NMR analysis that some competition exists between hydride ion transfer and cyanide ion transfer in the final step, and in fact, compound (25) was observed to be the major byproduct in the reaction. Also, much to⁵⁴ our surprise, the geometrical isomers (28) and (29) were partially separated by column chromatography. This result was partially inferred

via NMR analysis of the pertinent fractions. As a result, the sodium borohydride reduction follows a reduction-elimination-reduction sequence and the sodium cyanoborohydride reaction follows a reduction-elimination-addition sequence.



(28)



(29)

The sodium cyanoborohydride reduction reaction is unique in that, to our ⁵⁴ knowledge, this is the first example of a cyano group being incorporated into an organic substrate with this reagent. Moreover, the 3-cyanoenamines produced by this reaction have synthetic implications since they are potentially useful intermediates for the preparation of 1,4-dicarbonyl compounds and heterocycles. It is also suspected that the allylic amines may be useful due to their ability to form homoenoate anion equivalents ⁵⁹⁻⁶⁰ and due to their activity as antidepressant agents. ⁶¹ Thus, the 3-cyanoenamines or N,N-dimethylallylic amines may someday find industrial applications in the event one or more of these compounds is biologically active or very useful in important synthetic transformations.

In addition to investigating sodium borohydride and sodium cyanoborohydride as potential reducing agents of the vinamidinium salts, a myriad of other reducing agents was examined. These reducing agents are outlined below.

1. hydrogen gas + platinum oxide
2. sodium formate
3. sodium formate + palladium on charcoal
4. 3. above + catalytic amount of 18-crown-6
5. sodium sulfhydrate
6. lithium aluminum hydride @ r.t. and reflux
7. lithium monomethoxyaluminum hydride
8. lithium dimethoxyaluminum hydride
9. lithium trimethoxyaluminum hydride
10. borane-tetrahydrofuran complex
11. L-selectride; $(\text{sec-but})_3\text{-BH}^\ominus \text{Li}^\oplus$
12. Red-al; $(\text{MeOCH}_2\text{CH}_2\text{O})_2\text{-AlH}^\ominus \text{Li}^\oplus$
13. sodium dithionite; $\text{Na}_2\text{S}_2\text{O}_4$
14. sodium hydride

The above reducing agents were found to be unsuccessful for the reduction of vinamidinium salts because a major product was not obtained in sufficient yield. It is suspected that in some cases (e.g. ¹⁰⁻¹²~~j,k,l~~) the reducing agent could not gain the necessary proximity in order to transfer a hydride ion. Nonetheless, sodium borohydride and sodium cyanoborohydride were found to be excellent reducing agents for the vinamidinium moiety.

IV. CONCLUSIONS

The synthetic utility of Gold's reagent and vinamidinium salts was investigated in hopes of obtaining synthetically useful intermediates. Firstly, the reaction of p-nitrotoluene with Gold's reagent (Table VII) was optimized to an extent. The most favorable results were obtained using 30% excess sodium hydride, 50% excess Gold's reagent and a THF/ET₃N solvent system. This solution containing p-nitrotoluene was refluxed overnight and resulted in a 50% conversion and 90% yield. However, continued research should be pursued in the optimization of the reaction conditions for the preparation of nitroenamines.

Secondly, a series of arylvinamidinium perchlorates were successfully synthesized in excellent yields (Table VIII). Four of these six salts were selectively reduced by sodium borohydride and sodium cyanoborohydride to yield, respectively, N,N-dimethylallylic amines (25) and 2-aryl-3-cyanoenamines (27). Only one step was found to differ in the mechanism (Figure 11) of these reduction reactions, that is, the last step (Figure 12) where either a hydride ion or cyanide ion is transferred to the α,β -unsaturated iminium ion (23). Among the numerous reducing agents examined for the reduction of vinamidinium salts, only sodium borohydride and sodium cyanoborohydride were found to produce unique products which were not only characterizable, but also formed in good yields utilizing convenient separation techniques.

Finally, the research contained herein (Part II) was undertaken in hopes of obtaining useful products which may find application as industrial or laboratory intermediates.

V. RECOMMENDATIONS

The following is an outline of some suggestions for future research.

1. Additional conditions should be investigated concerning the reaction of p-nitrotoluene with Gold's reagent. Due to the mechanism of the reaction one should utilize a less polar solvent with a greater boiling point. For instance, 1,4-dioxane is less polar than THF and also has a higher boiling point (90°C vs 75°C). Also, one may wish to use a Lewis base as a cosolvent to enhance the removal of a proton from the intermediate. Some conditions along these lines are shown below.

	Solvent	Base	Temperature (°C)	Time (hrs.)
a)	dioxane/ ET_3N	NaH	reflux (90)	24
b)	dioxane/ ET_3N	NaH	reflux (90)	72
c)	dioxane/ ET_3N	NaOtBu	reflux (90)	24
d)	pyridine/iPrOH	NaOiPr	reflux (92)	24
e)	DMF	NaOMe	reflux (145)	24
f)	chlorobenzene/ ET_3N	NaOMe	reflux (118)	24
g)	N-methylmorpholine	NaH	reflux (115)	24

2. Upon optimization of the p-nitrotoluene/Gold's reagent reaction and the preparation of a series of activated (nitro) enamines

one should react one or more of the nitroenamines with a series of Grignard reagents in order to form substituted styrenes. This reaction with the substituted styrenes may find industrial applications in addition to forming substituted polystyrenes. A proposed mechanism for this reaction using p-nitrotoluene may be seen in (Figure 13). It has already been found by Gupton and Polk⁴⁰ that Gold's reagent reacts with Grignard reagents and lithium reagents in a similar manner.

3. In the workup procedure for the preparation of 2-aryl-vinamidinium perchlorates one may add the water directly to the flask with stirring, however, it is important that the flask and contents first be cooled to room temperature.

Also, one should use anhydrous sodium perchlorate rather than sodium perchlorate monohydrate to precipitate the salt since better yields were evidenced.

4. One may wish to expand the amount of reducing agents investigated for the reduction of the vinamidinium salts. The Red-al reaction could be repeated using dioxane as the solvent since it has a higher boiling point than THF. Also, one could repeat the lithium aluminumhydride reaction at room temperature for at least two days.

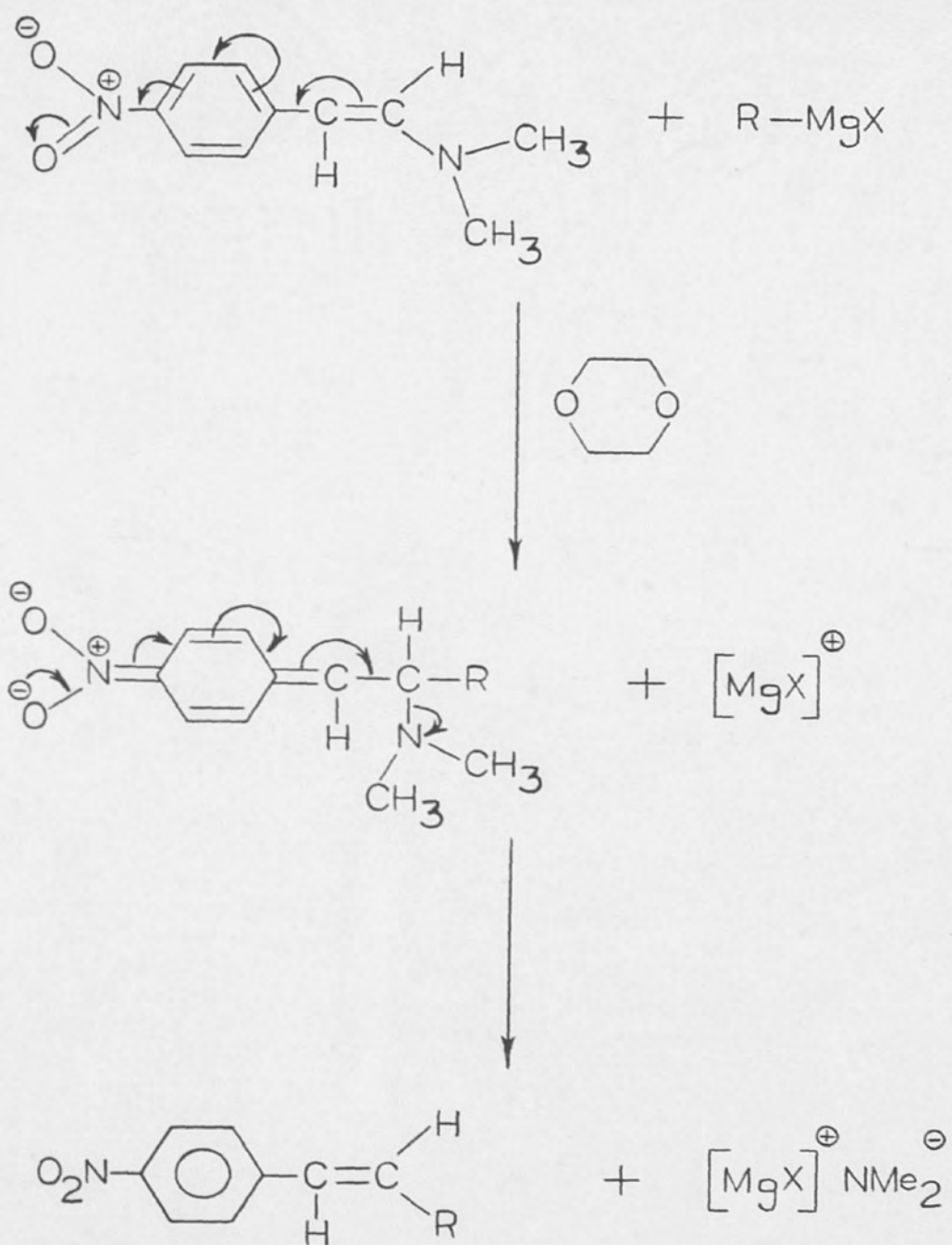


Figure 13. Proposed mechanism for the preparation of substituted styrenes from a nitroenamine and Grignard reagents.

INSTRUMENTATION AND EQUIPMENT

Removal of solvents in vacuo was performed using a Rinco Rotavapor rotary evaporator. Column chromatography was carried out using Mallincrodt SilicAR CC-7, 100-200 mesh silica gel in the ratio of about 30g silica gel per gram of mixture. Anhydrous sodium sulfate or magnesium sulfate was utilized as the drying agent in reaction workups.

Infrared spectra were recorded using a Perkin-Elmer 457 Grating Infrared Spectrophotometer and absorptions are reported in cm^{-1} . For spectra run with a solvent, sodium chloride cells were used where chloroform was the solvent. Nuclear magnetic resonance spectra were obtained at 60 MHz on a Varian EM-360A spectrometer. Chemical shifts were reported in ppm (δ) downfield from tetramethylsilane which was used as the internal standard. The abbreviations s, d, t, q and m refer, respectively, to singlet, doublet, triplet, quartet and multiplet, and coupling constants (J) are reported in Hz. Solvent systems used in obtaining NMR spectra include CDCl_3 , d^6 -DMSO and $\text{D}_2\text{O}/\text{DSS}$. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E spectrometer. Gas chromatographic analyses were carried out on a Perkin-Elmer 900 gas chromatograph using a 6' x $\frac{1}{4}$ ", 10% SE-30 on Chromosorb W column. All boiling points and melting points are uncorrected and a Fischer-Johns melting point apparatus was used for melting point determinations.

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